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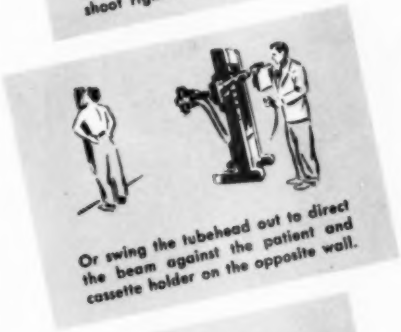

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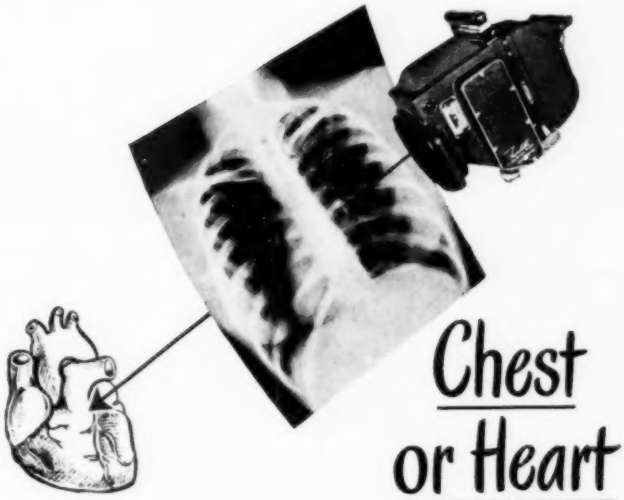

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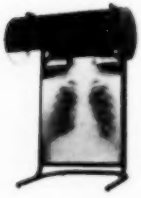

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VARIATION IN THE DURATION OF TUBERCULIN SKIN SENSITIVITY PRODUCED BY TWO STRAINS OF BCG[1,2]

RALPH F. JACOX AND GORDON M. MEADE

(Received for publication March 1, 1949)

INTRODUCTION

It is probable that the revived interest in the use of BCG vaccine as an auxiliary means for preventing tuberculosis will result in its more extensive employment. Any variable which might influence its success should be adequately controlled.

A recent experience of the writers with the administration of BCG to a group of nurses and medical students has brought to light a significant variable which is believed to be important. A BCG vaccine prepared in one laboratory was capable of causing a high percentage of tuberculin reactors, followed by a rapid loss of skin sensitivity to tuberculin. Another vaccine prepared in a different laboratory produced a prompt and sustained reactivity to tuberculin. These divergent results are thought to be related principally to some fundamental difference in the vaccines employed in this study. Moreover, it is felt that standardized methods of vaccine preparation and administration should be worked out before any extensive program of vaccination is planned.

METHODS AND RESULTS

In this study, two groups of individuals were vaccinated with BCG (Bacillus Calmette-Guerin) vaccine obtained from two different sources. Group A consisted of 103 nurses and medical students with an age distribution of 18 to 26 years. These individuals were vaccinated in September 1946 with a strain of BCG (Vaccine A) originally obtained from the Pasteur Institute and maintained in this country for several years. Vaccine A was made by a worker with long experience in preparation and use of BCG. It contained 15 mg. of bacteria in each ml., was shipped in refrigerated container, and arrived two days after preparation (twelve hours after leaving the laboratory of origin). Upon arrival it was immediately placed under refrigeration. Vaccination was then carried out twenty-four to forty-eight hours later by the percutaneous method described by Rosenthal (17).

All individuals were examined two weeks after vaccination and, with few exceptions, were noted to have developed a characteristic papular eruption at the site of inoculation. Tuberculin tests were performed at one-, three-, six-, nine-, and twelve-month intervals from the time of vaccination. The results of these tests are recorded in table 1.

[1] From the Department of Medicine of the University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals, Rochester, New York.

[2] Funds for this investigation came from the Helen W. Rivas Fund of the University of Rochester School of Medicine and Dentistry.

One month after vaccination, a well-developed skin sensitivity (2 or 3 plus)[3] to 0.005 mg. of PPD was observed in 88.3 per cent of the vaccinated individuals.

Three months after vaccination, 79.2 per cent reacted to 0.005 mg. of PPD. In addition, a decreased intensity of skin reaction was observed. Most of the vaccinated individuals had declined from a 2 or 3 plus reaction to one plus or a questionable reaction. In order to exclude decreased potency in the testing material as a cause for the decreased tuberculin reactions, 0.005 mg. of PPD and 1.0 mg. of O.T. were compared by injecting each substance into different sites on the same forearm. A more intense tuberculin reaction resulted when 1.0 mg. of O.T. was used. In all subsequent tuberculin tests, only O.T. (0.1 mg. followed by 1.0 mg. if 0.1 mg. gave a negative reaction) was employed for determining tuberculin sensitivity.

TABLE 1

Results of Vaccination with Vaccine A
Vaccinated September 1946 (103 Individuals)

MONTHS AFTER VACCINATION	NUMBER TESTED	NUMBER POSITIVE TO TUBERCULIN	PER CENT POSITIVE	NUMBER OF DOUBTFUL REACTIONS
1	103	91	88.3	9
3	101	80	79.2	9
6	98	38	38.7	18
9	69*	8	11.6	6
12	102	11	10.7	8

* One group of nurses comprising 33 individuals not tested at the nine-month interval.

Six months after vaccination, 38.8 per cent of the vaccinated individuals had a positive reaction to 1.0 mg. of O.T. The potency of tuberculin was again tested by comparing three different commercial tuberculins for ability to produce a positive skin reaction. No variation was detected, which seems to exclude the tuberculin as a factor responsible for the marked reduction in positive reactors.

The progressive decline in tuberculin skin sensitivity continued and nine months after vaccination only 11.6 per cent of Group A were positive reactors. Twelve months after vaccination, only 10.7 per cent had a positive tuberculin reaction to 1.0 mg. O.T. If those who had doubtful reactions are included, only 18.6 per cent demonstrated a positive tuberculin reaction one year after administration of Vaccine A.

Group B consisted of 178 medical students and nurses with the same age distribution as Group A. Of these, 100 had never received BCG vaccination. Seventy-eight of this group had been vaccinated in September 1946 with Vaccine A. They had previously developed a positive tuberculin reaction as a result of vaccination but had reverted to a negative reaction by the end of a year or less. All individuals in Group B were vaccinated in September 1947 with a vaccine prepared in another recognized laboratory. Vaccine B was made under carefully

[3] Tuberculin tests were classified according to criteria established in the 1940 edition of *Diagnostic Standards of Tuberculosis* of the National Tuberculosis Association.

controlled conditions and under the supervision of an individual who has had long experience in BCG preparation and use. This vaccine, containing 20 mg. of bacteria per cc., reached us (unrefrigerated) twenty-four to thirty-six hours after shipment. It was immediately placed under refrigeration and used twenty-four to ninety-six hours later. Vaccine B was administered in exactly the same manner as Vaccine A. Similarly, all individuals were observed two weeks after vaccination and were found to have developed a characteristic papular reaction at the vaccination site.

It was observed, however, that Vaccine B produced a more intense and prolonged local reaction than Vaccine A. Several individuals developed small, suppurating lesions at the vaccination site which persisted for several months. The increased local reaction occurred with the same frequency in the individuals vaccinated for the first time as in those revaccinated one year after a previous

TABLE 2

Results of Vaccination with Vaccine B
Vaccinated September 1947 (178 Individuals)

	MONTHS AFTER VACCINATION	NUMBER TESTED	NUMBER POSITIVE TO TUBERCULIN	PER CENT POSITIVE	NUMBER OF DOUBTFUL REACTIONS
Vaccinated first time	3	100	100	100.0	0
Revaccinated Group A reverters	3	78	78	100.0	0
Total	3	178	178	100.0	0
Vaccinated first time	12	100	93	93.0	5
Revaccinated Group A reverters	12	78	70	89.7	5
Total	12	178	163	91.5	10

vaccination with Vaccine A. It is of note, moreover, that none of those who were revaccinated showed any accelerated or Koch-like reaction to suggest that any residuum of sensitivity remained.

The duration of sensitivity in Group B was determined in the same manner as described for Group A (0.1 mg. of O.T. followed by 1.0 mg. if 0.1 mg. gave a negative reaction). As may be seen in table 2, 100 per cent of Group B were found to have developed sensitivity to tuberculin three months after vaccination. One year after vaccination, 91.5 per cent of those vaccinated still reacted to tuberculin with a clear-cut, positive skin test, 2.8 per cent had definitely negative reactions, and 5.7 per cent had doubtful reactions. Of the 91.5 per cent who were positive to tuberculin, 73.5 per cent reacted to 0.1 mg. of O.T., while the remainder required 1.0 mg. to elicit a positive reaction. It is apparent that the number of individuals in Group B who maintained a positive tuberculin sensitivity one year after vaccination is in decided contrast to the results obtained in Group A.

DISCUSSION

An accumulating experience in the use of BCG vaccine indicates that vaccination with this attenuated tubercle bacillus confers protection against tuberculous infection (1–12). Regardless of the problem of the mechanism of the development of resistance to tuberculosis following BCG vaccination, it appears likely, although not proved conclusively, that production of skin sensitivity to tuberculin is an important criterion for determining whether or not immunity has been enhanced by the procedure. It has been recommended, therefore, that vaccination be repeated until a positive tuberculin reaction results. Birkhaug (8) states, "clinical experience has taught that when allergy produced by BCG vaccination burns out in man, then his tuberculosis resistance falters and revaccination is necessary."

Holm (10) believes that effective vaccination must produce a positive tuberculin reaction and that the effect of vaccination lasts only so long as the positive tuberculin reaction persists. If one accepts Holm's and Birkhaug's premises, which it must be emphasized are not conclusively established, then it becomes of considerable importance to know the duration of sensitivity following BCG vaccination.

Holm (10) showed that a majority of vaccinated individuals were positive to 1.0 mg. of tuberculin four years after vaccination whether they existed in a tuberculous milieu or not. Similarly, Birkhaug (8) produced tuberculin sensitivity of long duration following percutaneous administration of BCG vaccine. Rosenthal, *et al.* (11) have reported sensitivity following percutaneous vaccination which persisted as long as six to eight years. Aronson (19), using intradermal administration, found that sensitivity probably persisted as long as eleven years.

It is clearly established, therefore, that in the hands of many workers BCG vaccine can confer a long-standing sensitivity to tuberculo-protein. The occurrence of such a short period of sensitivity as that following administration of Vaccine A in the present report was unexpected. The subsequent experience with administration of another vaccine indicates that the variable response is related to some inherent deficiency of the vaccine administered to Group A. The preparation of the two vaccines was essentially the same, as were the environmental conditions of each during the interval from preparation to administration. In fact, Vaccine B was subjected to more rigorous environmental changes than Vaccine A. The method of administration of vaccine was identical for each group.

Several different batches of Vaccine A were administered to Group A and in no instance did the unfavorable results appear to be related to a single ineffective ampule of vaccine. Moreover, the development of the sensitivity in 88 per cent of Group A one month after vaccination indicates that viable organisms were employed.

The possible influence of concentration of the vaccine suspensions cannot be ignored. Vaccine A contained 15 mg. of bacteria per cc. while Vaccine B contained 20 mg. per cc., representing 33 per cent more bacteria per unit of volume in the latter vaccine. Since Vaccine B produced local reactions associated with

a higher level of sensitivity, this suggests that a difference in size of inoculum may have been of importance. The effect of size of inoculum for establishing sensitivity of long duration has been previously demonstrated (15, 16). It should be pointed out, however, that the percutaneous method of vaccination of necessity permits a wide variation in the number of bacteria actually inoculated into each individual.

Forrsman (14) has indicated that the manner of vaccination is an important factor in the duration of sensitivity. Since Groups A and B were inoculated by the same technique, this variable can be eliminated from consideration.

A variable potency in the Old Tuberculin preparations used could explain the falling level of sensitivity observed in Group A. While facilities were not available for carrying out as extensive a standardization of tuberculin as Holm (13) recommends, the strengths of three different commercial preparations of O.T. were compared. No significant variation in tuberculin response was observed except when PPD was used. In this instance 0.005 mg. of PPD caused less reaction than 1.0 mg. of O.T. The use of PPD was therefore discontinued early in the study and only freshly prepared Old Tuberculin was administered to both groups. It is unlikely that the loss of sensitivity of Group A can be related to use of a faulty tuberculin.

There are inherent errors in the interpretation of the tuberculin reaction, especially when a low-grade sensitivity is present (4). The tuberculin reactions of Groups A and B were evaluated in as critical a manner as possible. No individual was said to have sensitivity to tuberculin unless an area of erythema measuring at least 5 by 5 mm. was present at the end of forty-eight hours.

Finally, after consideration of the foregoing variables, it becomes probable that a variation in some intrinsic factor in the vaccine accounts for the difference in duration of the induced sensitivity. Jensen (18) has shown the difficulty encountered by one laboratory in an attempt to strike a compromise between a BCG vaccine which produced too great a degree of local reaction and one which failed to produce sufficient reaction to confer sustained sensitivity. Aronson (5) has also suggested that a similar variation in potency of different lots of BCG may exist.

The results of this study appear to support the conclusion that a strain difference of BCG will influence the vaccine's effectiveness as a sensitizing agent. If sensitivity is a reflection of immunity, it is felt that a suitable method of control of the sensitizing potency of BCG vaccine should be set up.

SUMMARY

The tuberculin response of two groups of medical students and nurses following administration of BCG vaccine has been studied. In Group A (103 individuals vaccinated with vaccine A) positive skin reactions to tuberculin were observed in 88.3 per cent one month after vaccination; in 79.2 per cent three months later; and in only 10.7 per cent one year *after* vaccination. Group B (178 individuals) were vaccinated with vaccine B. Three months after vaccination, 100 per cent were positive to tuberculin and 91.5 per cent were positive at the end of one year.

The divergent results obtained with vaccines A and B appear to be related to a strain difference in the BCG used in preparation of the respective vaccines.

SUMMARIO

Variación en la Duración de la Cutisensibilidad a la Tuberculina Producida por Dos Cepas de BCG

La respuesta a la tuberculina fué estudiada en dos grupos de estudiantes de medicina y enfermeras después de la administración de vacuna BCG. En el Grupo A (103 individuos vacunados con vacuna A), evocáronse cutirreacciones positivas a la tuberculina en 88.3 por ciento al mes de la vacunación; 79.2 por ciento tres meses después; y sólo en 10.7 por ciento al año de la vacunación El Grupo B (178 individuos) fué vacunado con vacuna B, siendo positivos a la tuberculina 100 por ciento a los tres meses y 91.5 por ciento al año de la vacunación.

Los distintos resultados obtenidos con las vacunas A y B parecen relacionarse con una diferencia en las cepas de BCG usadas para la preparación de las respectivas vacunas.

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CORRELATION OF NUMBERS OF CUTANEOUS BCG VACCINATION PAPULES AND SUBSEQUENT TUBERCULIN ALLERGY AND TUBERCULOSIS RESISTANCE IN GUINEA PIGS[1]

KONRAD BIRKHAUG

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INTRODUCTION

A comparative study was made in 1944 (1) of the development of tuberculin hypersensitiveness and specific resistance in guinea pigs inoculated with BCG by the intracutaneous and scarification or multiple puncture methods. It was found that both methods produced a marked degree of tuberculin allergy as well as a significant resistance against a virulent tuberculous infection. It was noted, however, that the multiple puncture method stimulated tuberculin allergy more rapidly and resistance more effectively. On the basis of these findings, the multiple puncture method was applied to man either by the 8-needle fork (2) or the spring-actuated 40-needle apparatus (3). Between 1939 and 1946 more than 10,000 tuberculin-negative children and adults were thus vaccinated in the BCG Clinic at the Municipal Health Center at Bergen, Norway (4). Ninety-nine per cent acquired a positive tuberculin test within two months. The average duration of post-vaccination allergy was found to exceed four years, although occasionally it was lost as soon as one year. As of June 1948, about 80 per cent of the vaccinated group had been periodically followed with annual tuberculin tests and chest roentgenograms. The incidence of pulmonary tuberculosis was one-ninth of that observed among the nonvaccinated general population in Bergen during the same period. Up to the present more than 400,000 persons have been vaccinated throughout Norway. The intracutaneous injection method is used in many clinics while the multiple puncture method is used in others. Proponents of both methods claim equally good results. The latter method, however, is "preferred by about two-thirds of the doctors vaccinating with BCG in Norway," according to Hertzberg (5) and because "the intracutaneous injection may sometimes provoke troublesome local reactions, the percutaneous application (multiple puncture) of BCG has come into vogue." The method has been used exclusively in more than 6,000 BCG vaccinations performed in New York since 1946 under the auspices of the State Department of Health. But since both the injection and multiple puncture and scarification methods are used extensively throughout the world, their comparative efficiency remains a problem of some importance.

Furthermore, the question has been raised whether or not it is necessary to *inflict* as many as forty skin punctures. The following investigation was undertaken to answer that question.

EXPERIMENTAL

Materials and methods: Forty-five normal white albino guinea pigs, weighing 353 ± 34.36 Gm., which failed to react with 10 mg. Old Tuberculin injected intracutaneously, were used.

[1] From the Division of Laboratories and Research, New York State Department of Health, Albany, New York.

A 6 by 5 cm. skin area on the right side of linea alba, between the nipple and midsternum, was epilated with electric clippers and thoroughly washed with 95 per cent alcohol and dried with ether.

A 10-day-old Sauton culture of BCG (Lot No. B-23) showing typical surface growth, was decanted into a harvesting apparatus (6) and the semidry mass of BCG was homogenized and suspended in a dilution fluid that consisted of one part Sauton and three parts physiologic salt solution. The final vaccine contained 20 mg. BCG per ml. This suspension gave rise to 47 colonies on Löwenstein's egg medium seeded with a 10^{-6} dilution. Hence the vaccine contained 47 million viable microorganisms per mg. semidry weight. This same lot of vaccine was also used in man and gave rise to typical vaccination papules in the skin and positive tuberculin reactions within two months after vaccination.

Thirty guinea pigs, divided into ten equal groups, were vaccinated as follows: Each animal was held tightly by an assistant and a few drops of vaccine were spread evenly across the cleansed epilated skin with a sterile spatula. The sharp point of a 13-gauge sterile needle was pressed tangentially against the taut skin until it penetrated the epidermis at a depth of approximately 2 mm. By lifting the needle point vertically with a swift movement, the skin was torn open at the point where the needle had attached itself to the skin. Care was taken to avert free bleeding, but slight petechial bleeding occurred when the skin was stretched afterwards. While the skin still was held taut, a few more drops of vaccine were spread across the area and allowed to dry for two minutes. The animal was then returned to its cage. In this manner the ten groups of guinea pigs received respectively 1, 2, 4, 6, 8, 10, 15, 20, 30, and 40 skin punctures. The group receiving 6 punctures had 2 rows of 3 punctures each and the groups with 8 and 10 punctures two rows with 4 and 5 punctures in each. The groups receiving 15, 20, 30, and 40 punctures had parallel lines consisting of 5 punctures. An interspace of approximately 5 mm. was allowed between each puncture and each line. The remaining 15 guinea pigs were not vaccinated, but were kept under the same conditions as the experimental animals. All were housed in groups of 3, of the same sex, in metal cages (34 by 34 by 25 cm.) having closed sides and covered with a metal-framed 1 by 1 cm. mesh wire lid.

After three to five days, 1.0 to 1.5 mm. wide red punctate lesions appeared which during the following week enlarged into 2 to 4 mm. wide and 1 to 2 mm. high deeply injected papules. The underlying skin was then palpably indurated and the adjoining axillary and inguinal nodes were slightly enlarged in those animals which had received more than 15 punctures. During the third week the inflammatory reaction began to subside and desquamation followed with resorption of the papular elevations being nearly complete approximately forty days after vaccination. No suppuration occurred in the papules during this period and only a tawny pigmentation or pinhead scars indicated the healed vaccination sites. The lymphatic enlargement persisted for several months without softening or rupture through the overlying skin.

Post-vaccination tuberculin reactions: The tuberculin tests were performed intracutaneously with Old Tuberculin freshly diluted with saline to contain from 100 mg. to 0.001 mg. per ml. The reading was made after forty-eight hours and the minimum requirement for a positive reaction was definite induration or edema 10 mm. in diameter and 4 mm. thick when the skin was folded between caliper prongs. Half of this thickness multiplied by the two diameters of the indurated area (2 by 10 by 10 = 200 $mm.^3$) provided an estimate of the volume of the indurated area. When a positive reaction was obtained with 10 mg. O. T., the test was repeated with 1.0 mg. O.T. to determine the degree of tuberculin hypersensitiveness. The tuberculin tests were repeated at weekly intervals with gradually reduced concentrations of tuberculin during eight post-vaccination

weeks. Table 1 presents the data obtained on the rapidity and degree of tuberculin hypersensitiveness.

It may be seen from the data that the number of papules appears to be directly related to the promptness and degree of reaction to tuberculin and, furthermore, that the maximum reaction occurred in those animals that had received 40 separate intradermal inoculations. Every group that received 8 or more punctures had become tuberculin-positive two weeks following vaccination. The degree of

TABLE 1

Tuberculin Reactions

Average Volume of Induration 48 Hours after Intracutaneous Injection of Various Concentrations of Tuberculin

(Positive reaction ≧ 10 by 10 by 2 mm. (200 mm³) induration)

(5 guinea pigs in each group)

WEEKS AFTER VACCINATION	CONCENTRATION OF OLD TUBERCULIN "MG."	NUMBER OF BCG PAPULES									
		1	2	4	6	8	10	15	20	30	40
1	10	0	0	0	0	0	39	43	74	98	102
2	10	0	0	0	103	261	271	316	451	532	552
3	10	0	0	64	274	261	314	432	468	581	546
4	10	0	0	135	358	393	—	—	—	—	—
5	10	0	112	259	—	—	—	—	—	—	—
6	10	0	184	—	—	—	—	—	—	—	—
7	10	98	148	—	—	—	—	—	—	—	—
8	10	113	—	—	—	—	—	—	—	—	—
Quantitative degree of tuberculin hypersensitiveness											
3	1.0	0	0	0	104	150	250	276	266	278	331
4	0.1	0	0	0	172	178	124	184	168	181	202
5	0.01	0	0	0	154	182	196	222	213	256	270
6	0.001	0	0	0	0	0	0	36	59	108	136
7	0.0001	0	0	0	0	0	0	0	0	45	74
8	1.0	0	0	21	114	189	261	352	382	332	341
8	1.0 BCG OT	0	0	72	150	185	286	383	455	512	542

reactivity of the animals could be determined both by estimating the size of the area of induration and by modifying the dose of O.T. used.

Response to the inoculation of virulent tubercle bacilli: Sixty-five days after vaccination the 30 experimental and 15 nonvaccinated control guinea pigs were injected subcutaneously in the right hind leg with 0.0001 mg. of a virulent strain of human tubercle bacilli (No. 33246) from a month-old Löwenstein egg medium culture. This dose gave rise to 1,172 eugonic colonies on a series of Löwenstein egg medium tubes after 10 weeks' incubation. The weight of the immunized animals when challenged was 621 ± 60.47 Gm., and that of the controls 589 ± 57.16 Gm.

Eight weeks later all were retested with 10 mg. O. T. intracutaneously and the reactions read as before. The immunized animals all reacted strongly with

an average induration measuring 1,819 ± 654.4 mm.^{2} and central necrosis occurred in about 50 per cent of these lesions. The most severe reactions were found among the animals that had received fewer than 15 punctures (2,278 ± 566.2 mm.^{2} induration and 125 ± 42.3 mm.^{2} central necrosis). Those with 20 or more punctures had 1,236 ± 447.3 mm.^{2} induration and 51.7 ± 12.8 mm.^{2} central necrosis. The control group showed 2,768 ± 867.9 mm.^{2} induration and 261.2 ± 42.1 mm.^{2} central necrosis.

The weight of the immunized animals was now 706 ± 59.21 Gm., and that of the control animals 627 ± 63.12 Gm.

The right inguinal lymph nodes were definitely larger in the control than in the immunized groups. Among the latter it was noted that the nodes were larger in the animals that received fewer than 15 punctures than in those with more.

Three control animals succumbed with intercurrent gastrointestinal infection 64, 64, and 65 days after challenge. Of the remaining 12, 6 died with generalized tuberculosis 74, 107, 118, 118, 121, and 132 days after inoculation. The other 6 were killed 163 days after inoculation. Among the immunized groups 6 died with generalized tuberculosis. Two of these had received a single BCG inoculation, 2 others had received but 2 inoculations, and the other 2 had received 4 and 6 inoculations. These animals died at approximately the same time as the controls.

Measurement of tuberculous hyperplasia: As previously described (7), necropsy was delayed until the animal had remained for several hours in the refrigerator (2° to 3°C.) in order to allow the blood to coagulate. This ensures uniformity in the assessment of the volume and weight of various lymph nodes and organs. The major lymph nodes (table 2) were carefully dissected free from contiguous tissues and their volume was determined by water displacement in specially constructed volumetric cylinders calibrated to 0.001 ml. The volume of the spleen, liver, and lungs was determined in the same manner. Finally, the weight of these organs and the pooled lymph nodes (total lymph nodes) was expressed in per cent of the animal's body weight in order to obtain objective data on the degree of tuberculosis in the immunized and control groups of animals. The completed data were then submitted to statistical treatment for significance according to Fisher's (8) method for comparison of two means.

The data showing the weight of the animals and of lymph nodes, spleen, liver, and lungs for each group of the immunized animals are graphically shown in the figures. For purposes of clarity, the vaccinated animals that had received 1, 2, 4, and 6 inoculations have been pooled (group I). Those that had received 4, 6, 8, and 10 inoculations constitute group II. Those with 8, 10, 15, and 20 inoculations are shown as group III, and those that received a greater number of inoculations have been pooled as group IV.

Tuberculous hyperplasia in lymph nodes: The results, which afford a comparison of the volume of the various groups of lymph nodes, have been collected in table 2, with an expression of the probability that the observed differences are significant. It will be noted that the least hyperplasia occurred in group IV, those animals which had received the greatest number of inoculations of vaccine.

TABLE 2

Tuberculous Hyperplasia in Lymph Nodes from Animals Immunized with 1, 2, 4, 6 (I), 4, 6, 8, 10 (II), 8, 10, 15, 20 (III), 15, 20, 30, 40 (IV) BCG Papules and from Control Tuberculous Infection Animals (V)

Statistical Analyses of Volume (in ml.) of Nodes from 12 Animals in each Group

LYMPH NODES	GROUPS OF ANIMALS					PROBABILITY							
	I	II	III	IV	V	I vs V		II vs V		III vs V		IV vs V	
	Volume in ml.					*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*
Sup. inguinal.....Left	0.11	0.11	0.21	0.10	0.21	1.509	0.15	1.372	0.18	0.588	0.59	0.933	0.38
Sup. inguinal.....Right	0.99	0.61	*0.42*	*0.32*	0.81	0.429	0.68	0.473	0.65	*10.616*	<0.001	*13.389*	<0.001
Deep inguinal.....Left	0.01	0.01	0.01	0.01	0.01	0.220	0.80	0.036	>0.90	0.020	>0.90	0.042	>0.90
Deep inguinal.....Right	0.57	0.33	*0.16*	*0.10*	0.59	0.956	0.38	1.691	0.12	*2.849*	0.01	*3.355*	0.01
Iliac.....Left	0.91	0.80	0.57	0.29	0.56	0.588	0.59	0.142	0.88	0.064	>0.90	1.847	0.08
Iliac.....Right	1.15	0.95	0.52	0.29	0.78	1.381	0.18	0.681	0.51	1.125	0.27	2.205	0.04
Periportal.....	1.14	0.71	0.40	*0.12*	0.97	0.556	0.59	0.858	0.40	0.967	0.07	*3.276*	<0.01
Retrorenal.....	1.76	1.75	1.23	*0.69*	1.16	2.021	0.06	2.651	0.01	0.316	0.75	*2.893*	0.01
Trach. bronch.....Left	1.88	1.42	*0.82*	*0.44*	1.35	2.791	0.02	0.387	0.71	*2.887*	<0.01	*5.158*	<0.001
Trach. bronch.....Right	1.83	1.53	1.00	*0.57*	1.38	2.259	0.04	0.848	0.40	2.117	0.04	*5.519*	<0.001
Cervical.....Left	0.15	0.13	*0.12*	*0.11*	0.21	1.834	0.08	2.482	0.02	*3.380*	<0.01	*3.756*	<0.001
Cervical.....Right	0.15	0.16	0.15	*0.11*	0.22	2.156	0.04	1.303	0.21	1.617	0.12	*3.011*	<0.01
Axillary.....Left	0 08	0.10	0.11	0.09	0.12	1.252	0.21	0.608	0.51	0.311	0.75	0.980	0.35
Axillary.....Right	0.09	0.11	0.11	0.09	0.14	1.218	0.22	0.698	0.49	0.686	0.50	1.264	0.22
Total lymph nodes in grams.....	7.88	7.98	5.53	*3.44*	7.28	0.965	0.36	0.564	0.59	1.453	0.16	*3.588*	<0.01
Efficiencies in per cent.....						0		0		26.7		60.0	

N.B. In Fisher's 1938 tables for distribution of *t* (quotient expressing the deviation as a multiple of its probable error), we observe that a $P \leq 0.01$ (probability that the observed mean deviation bearing this or smaller values cannot have occurred by chance alone) requires that $t \geq 2.819$ when each group contains 12 animals or samples. Every difference having *absolute significance* is italicized in tables 2 and 3.

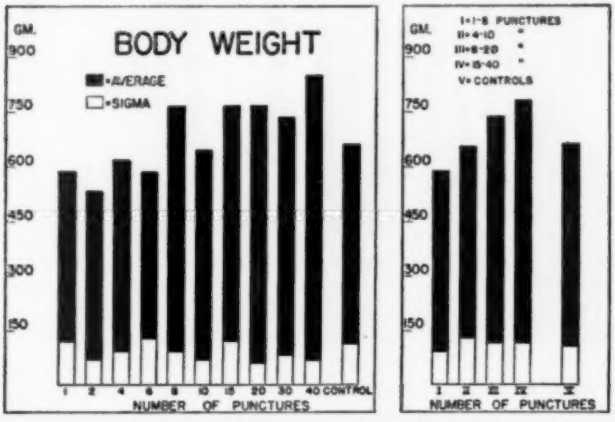

FIG. 1. Average body weight at autopsy of vaccinated and control guinea pigs. (Left) Single groups of animals vaccinated with 1 to 40 skin punctures. (Right) Pooled groups of vaccinated animals.

It may also be noted that marked difference existed between the size of the inguinal nodes in the right and left groups. Judged by the criterion of lymph node hyperplasia, therefore, those guinea pigs that had received 10 or fewer injections

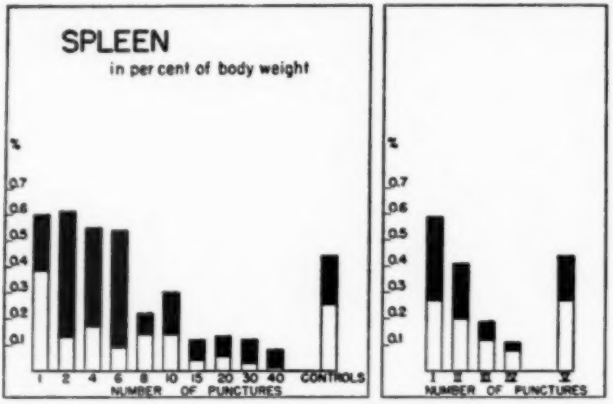

FIG. 2. Average weight of spleen expressed in per cent of body weight of vaccinated and control guinea pigs.

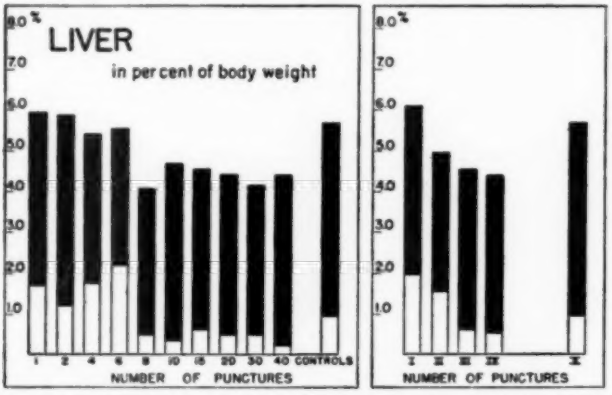

FIG. 3. Average weight of liver expressed in per cent of body weight of vaccinated and control guinea pigs.

of BCG did not display resistance to the challenging inoculation. The animals which had received a greater number of inoculations showed such resistance.

Spleen, liver, lungs, and lymph nodes: Similar measurements have been made of the spleen, liver, and lungs of all the animals. The values, again expressed in volume, weight, and in percentage of body weight, have been collected in table 3. It is evident that by these standards the spleens and lungs of the animals

that had received the greater number of vaccination reactions differed significantly from the control animals and from those experimental guinea pigs that had received fewer inoculations. The livers, on the other hand, showed no such

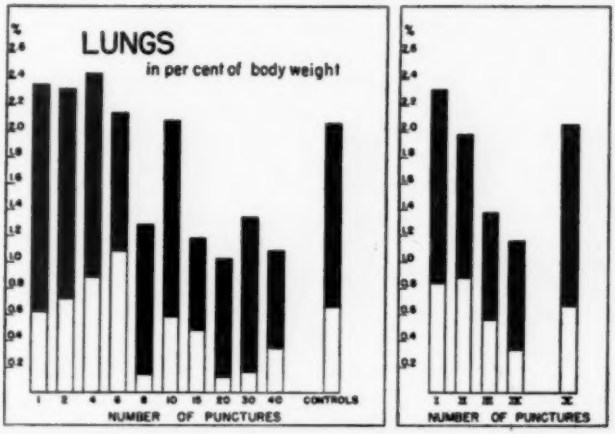

FIG. 4. Average weight of lungs expressed in per cent of body weight of vaccinated and control guinea pigs.

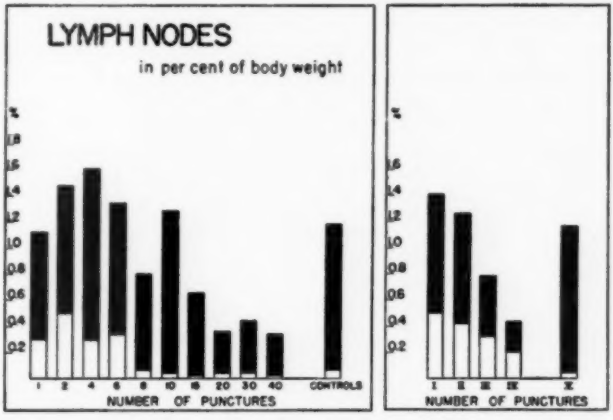

FIG. 5. Average weight of pooled lymph nodes expressed in per cent of body weight of vaccinated and control guinea pigs.

differences excepting when calculated as percentage of total body weight. By this criterion the lungs also indicated significant deviation.

Petroff and Steenken score: The lesions have also been graded according to the scheme suggested by Petroff and Steenken (9). The data are summarized in

TABLE 3

Tuberculous Hyperplasia in Spleen, Liver, and Lungs
Statistical Analyses of Weights, Volumes and Weights Expressed in Percentage of Body Weight
12 Animals in Each Group

ORGANS	GROUPS OF ANIMALS					PROBABILITY							
	I	II	III	IV	V	I vs V		II vs V		III vs V		IV vs V	
	Average					*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*
Body Gm.	589	609	735	782	667	1.587	0.13	1.401	0.18	1.482	0.16	*2.375*	0.01
Spleen Gm.	3.16	2.53	1.35	*0.84*	2.78	1.180	0.27	0.419	0.52	2.622	0.02	*4.038*	<0.001
Spleen ml	3.10	2.45	1.33	*0.85*	2.70	1.936	0.07	0.421	0.68	2.516	0.02	*3.851*	<0.001
Liver Gm.	35.73	31.19	32.33	33.77	36.16	0.149	0.89	2.120	0.04	1.671	0.11	1.063	0.30
Liver ml.	33.38	29.13	30.96	32.25	33.17	1.387	0.19	1.666	0.12	0.956	0.38	0.392	0.72
Lungs Gm.	12.67	12.26	9.90	*8.78*	13.41	0.566	0.59	0.809	0.41	2.568	0.02	*3.398*	<0.01
Lungs ml.	14.68	14.40	*12.41*	*10.89*	17.21	1.681	0.11	1.691	0.11	*2.972*	0.01	*4.978*	<0.001
Weights expressed in percentage of body weight													
Spleen per cent.	0.58	0.40	0.19	*0.11*	0.44	2.303	0.03	0.375	0.71	2.612	0.02	*3.807*	<0.001
Liver per cent.	6.04	4.91	*4.40*	*4.89*	5.56	1.328	0.20	1.220	0.25	*3.655*	0.01	*3.780*	<0.001
Lungs per cent.	2.31	1.98	1.39	*1.16*	2.06	0.980	0.38	0.247	0.78	2.651	0.02	*4.239*	<0.001
Lymph nodes per cent.	1.41	1.27	0.78	*0.46*	1.19	2.009	0.05	0.306	0.75	1.642	0.12	*3.118*	<0.01
Efficiencies in per cent						0		0		18.2		81.8	

TABLE 4

Macroscopic Scoring of Tuberculous Involvement in Vaccinated and Control Guinea Pigs
(*Ad modum* S. A. Petroff and W. Steenken, Jr., J. Immunol., 1930, *19*, 79)

ANIMAL GROUPS	NUMBER OF ANIMALS	TUBERCULOUS INVOLVEMENT							
		++++		+++		++		+	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Control	12	4	33.3	6	50.0	2	16.7	0	0
Vaccinated I	12	2	16.7	10	83.3	0	0	0	0
Vaccinated II	12	1	8.3	8	66.7	3	25.0	0	0
Vaccinated III	12	0	0	3	25.0	3	25.0	6	50.0
Vaccinated IV	12	0	0	0	0	0	0	12	100.0
Vaccinated:									
Punctures 1	3	1		2		0		0	
Punctures 2	3	0		3		0		0	
Punctures 4	3	0		3		0		0	
Punctures 6	3	1		2		0		0	
Punctures 8	3	0		1		2		0	
Punctures 10	3	0		2		1		0	
Punctures 15	3	0		0		0		3	
Punctures 20	3	0		0		0		3	
Punctures 30	3	0		0		0		3	
Punctures 40	3	0		0		0		3	

\+ = tuberculous lesions at the site of inoculation, with or without lymph node involvement, with few tubercles in lungs and spleen.

++ = tubercles in 2 or 3 organs, such as spleen, liver, lungs, and lymph nodes.

+++ = generalized tuberculosis, as well as extensive active disease, such as tuberculous pneumonia.

++++ = fulminating and generalized tuberculosis, with multiple and large infarcts in spleen and liver, multiple cavernous and confluent tuberculosis in lungs, with heavy involvement of lymph nodes, ruptured spleen, and allergic phenomena.

table 4. It may be seen that one-third of the control animals had fulminating and generalized tuberculosis (4+) with suppuration at the site of inoculation. Multiple and confluent infarcts in the spleen and liver, multiple cavernous and confluent tuberculosis in the lungs, and generalized caseonecrotic hypertrophy of lymph nodes were common. Half of the control animals showed generalized tuberculosis with somewhat less involvement (3+) and the rest showed tuberculosis of the lymph nodes, spleen, liver, and lungs.

The animals which had been vaccinated with from 1 to 8 inoculations did not differ significantly from the controls but those which had received 10 or more showed less tuberculosis; this was still more pronounced in the animals that had received 15 inoculations. In them only tuberculosis in the regional lymph nodes (1+) and an occasional discrete tubercle in the spleen or lung were found. The results confirmed the measurements of organ size and weight and allergy in showing the improved status of the animals that had received the largest number of vaccinations.

DISCUSSION

The data leave little room to doubt that in the case of experimental tuberculosis in the guinea pig the promptness and extent of tuberculin allergy is related to the size of the BCG vaccination and that resistance to infection increases with the number of individual inoculations and the number of BCG microorganisms inoculated. In these experiments the duration of allergy has not been measured. It will be remembered that Törnell (10) found that the duration of tuberculin allergy was also related to the size of the vaccination reaction. It would seem, therefore, that the larger number of papules currently being recommended for percutaneous vaccination is thoroughly supported by experimental evidence.

SUMMARY AND CONCLUSIONS

The multiple puncture method of BCG vaccination produced in guinea pigs the most rapid and intense tuberculin allergy when 15 or more punctures were made through skin moistened with 20 mg. per ml. BCG vaccine. The best tuberculin allergy was produced by 40 BCG vaccination papules.

A significant resistance to a virulent tuberculous infection was acquired by guinea pigs having received 15 or more punctures. The most effective specific immunity was produced by 40 BCG vaccination papules.

It is recommended, therefore, that the practice of 30 to 40 percutaneous punctures in BCG vaccination of both children and adults be continued in order to produce the most rapid allergy and durable resistance to tuberculous disease.

SUMARIO Y CONCLUSIONES

Correlación entre el Número de Pápulas Cutáneas en la Vacunación BCG y la Subsiguiente Alergia a la Tuberculina y Resistencia a la Tuberculosis en el Cobayo

La técnica de la multipunción para la vacunación con BCG produjo en los cobayos la más rápida e intensa alergia tuberculínica cuando se hacían quince o más punciones a través de piel humedecida con 20 mg. por cc. de vacuna BCG.

La mejor alergia a la tuberculina fué producida por cuarenta pápulas en la vacunación con BCG.

Resistencia significativa a una infección tuberculosa virulenta fué adquirida por cobayos que recibieron quince o más punciones. La más efectiva inmunidad específica fué producida por cuarenta pápulas de vacunación BCG.

Recomiéndase, por lo tanto, que, a fin de producir la alergia más rápida y resistencia duradera a la afección tuberculosa, continúe, tanto en niños como adultos, la costumbre de hacer treinta a cuarenta punciones percutáneas en la vacunación con BCG.

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LUNG TRAUMA AT PNEUMOTHORAX INDUCTION[1]

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INTRODUCTION

Induction of artificial pneumothorax is a simple procedure which in the great majority of instances is attended by little discomfort and no complications. Most physicians experienced in pneumothorax therapy, however, have observed serious and at times alarming complications at induction, the most important being air embolism and perforation of the lung.

The literature indicates the considerable difference of opinion which exists concerning the frequency of lung rupture at the time of pneumothorax induction. The early workers, Brauer (1), Robinson and Floyd (2), Balboni (3), and others, considered traumatic pneumothorax avoidable with good technique. Morgan (4), on the other hand, believed as long ago as 1914 that the first intrapleural readings obtained are those of a traumatically induced space. There has been much controversy regarding the type of needle which might cause or prevent lung puncture (Jones (5), Tchertkoff and co-workers (6, 7, 8, 9)). Karan (10) observed roentgenographic evidence of rupture of the lung following induction of pneumothorax in 9 of 70 patients, or 13 per cent, and Rubin (11) stated in 1937 that "lung injury is the rule rather than the exception in pneumothorax treatment, particularly at the time of induction." Rubin pointed out the fact that often rupture cannot be verified clinically and that in most instances it is not followed by immediate serious consequences. These are usually lung perforations of the "closed," not valvular, variety which close quickly aided by the relaxing effect of the pneumothorax. A pneumothorax space has often been demonstrated by roentgenography or fluoroscopy after a supposedly unsuccessful attempt at induction. Examples of this have been cited by Ornstein and co-workers (12). Using the formula of Coryllos (13), Ornstein and his associates (12) calculated the volume of gas present in the pleural cavity twenty-four hours after induction; in 5 cases they found an increase over the volume of air which had been injected of from 115 to 2,170 cc. Alexander (14) has stated that "a puncture of the visceral pleura with the pneumothorax needle is largely preventable." Ustvedt (15) believes injury to the lung during induction to be a "very common occurrence." Mattill and Jennings (16) reviewed a large series of traumatic pneumothoraces and found that lung perforation had occurred at induction in 2 per cent of cases with unilateral pneumothorax and in 10 per cent of inductions in cases where pneumothorax was already present on the other side. In the majority of the unilateral cases, symptoms were slight or absent. In most of the bilateral cases, symptoms were severe enough to require needle deflation or catheter drainage, and in the bilateral group the lung rupture was fatal in 5 instances.

The present writers were stimulated to reinvestigate the problem of lung trauma at pneumothorax induction by the occurrence of a nearly fatal lung perforation which was seen at the Montefiore Hospital Sanatorium.

H. D., a 44-year-old man with far advanced bilateral fibrocaseocavernous pulmonary tuberculosis, had been receiving left artificial pneumothorax treatment for two years.

[1] From the Montefiore Hospital Country Sanatorium, Bedford Hills, New York.

The pulmonary collapse was complicated by apical adhesions which could not be severed. The therapy was clinically effective, however, and because of extensive contralateral disease and the inadvisability of performing thoracoplasty the pneumothorax had been maintained. The lesions in the right lung progressed and excavated. On July 26, 1948 right artificial pneumothorax was induced. No difficulty was encountered at induction and pleural readings with good oscillations were obtained immediately. The initial pressures were −14 −9 cm. of water; final pressures after administration of 250 cc. of air were −10 −4. The patient was seen three hours later and appeared comfortable. Six hours after induction he experienced increasing dyspnea and preparations were made to decompress the right pleural cavity. As the decompression needle was about to be inserted, the patient's condition suddenly became alarming. His dyspnea increased, he was cyanotic, and there was tachycardia with a rate of 140 per minute. A 19-gauge needle was inserted into the right pleural cavity, pressures, of −10 +10 were recorded, and air was removed. A few minutes later the patient was severely dyspneic, intensely cyanotic, his radial pulse was almost imperceptible, and his skin was cold and clammy. He became comatose and appeared moribund. A 19-gauge needle was immediately inserted into the left pleural space. Positive pressure was recorded here also (−40 +10) and the left pleural space was decompressed. The patient was placed in an oxygen tent, and air under pressure was repeatedly aspirated from both pleural cavities. His condition improved and after removal of 2,000 cc. of air from the left chest the pressure readings on this side became and remained negative. The right lung continued to leak air and to build up tension in the right pleural cavity. After removal of about 7,000 cc. of air from that side, with pressures repeatedly returning to highly positive after each aspiration, an indwelling needle was inserted with subaqueous drainage. Continuous decompression was maintained for eleven hours, at the end of which time observation indicated closure of the perforation. One gram of streptomycin and 500,000 units of penicillin were instilled into the pleural space and the needle was removed. The patient's subsequent course was uneventful. No attempt was made to maintain the pneumothorax on the right side, and the patient was given streptomycin intramuscularly in dosage of one gram daily for two months. This was followed by regression of the lesions in the right lung and sputum conversion. The left pneumothorax was continued.

This dramatic occurrence resulted from perforation of the right lung at the time of induction. One may speculate that removal of the support of the chest wall by the creation of a pneumothorax permitted an emphysematous bleb to rupture or an adhesion to tear at its visceral junction, but actual trauma to the lung by the induction needle is the more likely explanation.

In 29 inductions performed at Sea View Hospital, Selikoff and Tchertkoff (9) noted appreciable dyspnea in 40 per cent, and 14 per cent of their patients required pleural decompression following induction of pneumothorax. These authors postulated that every induction is accompanied by traumatic pneumothorax and that injury to the lung is unavoidable. They attempted to demonstrate this by taking radiograms of the chests of patients after needling the pleural space without introducing air. In their clinical material and with their technique (6, 7, 8, 9) they did in fact show that every induction was first a traumatic one. In 19 consecutive cases simple needling of the pleural space produced pulmonary collapse in every instance, varying in extent from 5 to 90 per cent. On the basis of these findings, they recommended that pneumothorax should be induced by lung puncture purposefully produced with a fine-gauge needle. They consider this method least likely to produce a severe tear of the lung. In reviewing their data (7), it is apparent that the intrapleural pressures recorded were unsatisfactory in 5 of the 19 cases. Furthermore, the clinical material at

Sea View Hospital, a municipal institution, is probably not typical of sanatorium patients generally. Unpublished observations on a large number of pneumothorax inductions performed at the Montefiore Hospital Sanatorium during the last two years reveal a much lower incidence of significant lung trauma. In patients with a free pleural space, initial pneumothorax treatment was followed by symptoms and fluoroscopic findings indicative of definite lung perforation in 3.33 per cent, an incidence one-twelfth that reported by Selikoff and Tchertkoff.

The present investigation has been conducted to evaluate the validity of the assumption that significant lung damage is unavoidable during pneumothorax induction.

MATERIAL AND METHODS

A series of 23 consecutive unselected sanatorium patients who required pneumothorax therapy for control of active pulmonary tuberculosis forms the basis of this study. Thirteen of them were females and 10 males. Their ages ranged from 19 to 42 years. Twenty had moderately advanced tuberculosis and 3 had far advanced disease. In 8 the lesions were unilateral, in 15 bilateral, and 22 had patent cavities (table 1).

The patients were prepared for induction of pneumothorax in the usual manner, and the induction needle was inserted carefully until intrapleural readings with respiratory oscillations were obtained on the manometer.[2] Patients were not urged to breathe deeply. When readings had been obtained, the needle was removed. No air was introduced into the pleural cavity. A postero-anterior roentgenogram of the chest was made in expiration three or six hours later and again twenty-four hours after pleural puncture. In 6 patients (Cases 18, 19, 20, 21, 22, and 23, table 1) expiration films were also made in left anterior and right anterior oblique projections. The films were then inspected for evidence of pneumothorax. Some patients were also fluoroscoped, but expiration films have been found to be more satisfactory, especially in thick-chested individuals. After the twenty-four-hour film had been obtained, pneumothorax was induced and at this time air was allowed to enter the pleural cavity from the pneumothorax apparatus. All punctures were performed with a Fischer[3] induction needle. It is felt that similar results could probably be obtained with a 19-gauge short-beveled needle. However, a sharp cutting-edge cannula and dull obturator combination, like the Fischer, Solomon, or Kuss induction needle, is a little safter for those without great experience because there is less danger of grossly overshooting the mark in the process of forcing a dull needle through thick skin or endothoracic fascia.

RESULTS

The needling of the space without introduction of air produced the following results. None of the 23 patients became dyspneic. In 21 of the 23 no pneumo-

[2] A Zavo·l or a Davidson pneumothorax apparatus was used in all cases.

[3] This consists of a 14-gauge sharp outer cannula and a 17-gauge 3-inch needle with blunt tip which is inserted through the cannula for the pleural puncture. (B-D Catalogue No. LL1, p. 23, items nos. 475 LNRA and 475 LNRB. Becton, Dickinson and Co., Rutherford, New Jersey).

thorax space could be seen on expiration films taken three, six, and twenty-four hours later. All 23 patients had unobliterated pleural spaces as shown by the intrapleural readings (table 1) and by the successful induction of pneumothorax performed twenty-four hours later. One of the patients, Case 1, had a traumatic pneumothorax requiring decompression after the second pleural puncture, but not after the first. Her intrapleural pressures were −13 −9 cm. of water at the

TABLE 1

Intraplural Pressures in 23 Consecutive Initial Pleural Punctures, with and without Administration of Air

CASE NUMBER	ROENTGENOGRAPHIC CLASSIFICATION OF LESIONS			INTRAPLEURAL READINGS			
	Distribution	Extent	Predominant Types	First needling*	Second needling†		
				Reading in cm. of H_2O	Reading in cm. of H_2O	Amount of air in cc.	Reading in cm. of H_2O
1. H. S.	Unilateral	Mod. adv.	Caseocavernous	−13 −9	−13 −9	200	−5 −3
2. J. B.	Bilateral	Mod. adv.	Caseocavernous	−8 −6	−8 −6	200	−4 −2
3. A. W.	Bilateral	Mod. adv.	Fibrocaseocavernous	−10 −6‡	−12 −8	300	−6 −4
4. L. C.	Bilateral	Far adv.	Fibrocaseocavernous with contralateral pleuritis	−10 −6‡	−7 −3	250	−5 −2
5. M. A.	Bilateral	Mod. adv.	Caseocavernous	−12 −10	−13 −9	250	−8 −2
6. A. C.	Unilateral	Mod. adv.	Caseocavernous	−10 −7	−10 −6	300	−8 −4
7. S. S.	Unilateral	Mod. adv.	Caseocavernous	−10 −7	−10 −8	300	−6 −5
8. L. F.	Bilateral	Mod. adv.	Caseocavernous	−8 −6	−5 −3	250	−4 −2
9. F. D.	Bilateral	Mod. adv.	Caseocavernous	−13 −8	−13 −7	300	−10 −5
10. S. K.	Bilateral	Mod. adv.	Caseocavernous	−7 −4	−8 −4	125	−5 −2
11. A. R. C.	Unilateral	Mod. adv.	Caseocavernous	−11 −10	−11 −5	250	−7 −1
12. K. H.	Unilateral	Mod. adv.	Caseocavernous	−7 −4	−7 −2	250	−5 −1
13. B. H.	Bilateral	Mod. adv.	Fibrocaseocavernous	−9 −7	−12 −10	300	−7 −2
14. A. L.	Bilateral	Mod. adv.	Fibrocaseocavernous	−12 −8	−7 −3	300	−7 −2
15. W. P.	Unilateral	Mod. adv.	Caseocavernous	−9 −5	−10 −8	300	−9 −6
16. F. K.	Bilateral	Mod. adv.	Fibrocaseocavernous	−8 −5	−9 −5	250	−8 −2
17. E. T.	Bilateral	Mod. adv.	Caseocavernous	−12 −11	−12 −9	250	−7 −5
18. E. L.	Bilateral	Far adv.	Fibrocaseocavernous with bilateral pleuritis	−6 −4	−7 −4	250	−6 −3
19. R. W.	Unilateral	Mod. adv.	Caseocavernous	−9 −7	−8 −7	250	−5 −3
20. M. T.	Unilateral	Mod. adv.	Caseocavernous	−5 −3	−5 −3	300	−3 −1
21. Hy. S.	Bilateral	Mod. adv.	Fibrocaseocavernous	−11 −7	−10 −5	250	−5 −3
22. S. L.	Bilateral	Far adv.	Fibrocaseocavernous	−11 −7	−13 −7	300	−7 −3
23. I. S.	Bilateral	Mod. adv.	Fibrocaseous, with contralateral pneumothorax	−10 −5	−13 −5	150	−11 −4

* No air given.

† Performed 24 hours later. Air was administered at this time.

‡ "Traumatic pneumothorax"

time of experimental needling, and roentgenograms three and twenty-four hours later showed no pneumothorax space. After the twenty-four-hour film had been taken pressures were again found to be −13 −9 (table 1) and at this time air was given. Lung perforation followed the latter puncture.

Two of the 23 patients showed the presence of air intrapleurally on the roentgenograms obtained after needling alone (Cases 3 and 4, table 1). The extent of collapse was 10 per cent of the right upper lobe in Case 3 and 20 per cent of the right upper lobe in Case 4. In these 2 cases traumatic pneumothorax had undoubtedly occurred. No symptoms were noted in either patient.

The question arises as to how much air must be in a pleural space for it to be

visible? Tchertkoff (6) states that less than 150 cc. cannot be detected by any roentgenographic technique. Accordingly, 12 patients were examined roentgenographically twenty-four hours after induction with 150 to 300 cc. of air. In all of these patients the pneumothorax space was clearly visible on an expiration film made twenty-four hours later (table 2). This is not inconsistent with Tchertkoff's estimate. Visualization of amounts less than 150 cc. was not attempted. Left anterior oblique and right anterior oblique films were made in expiration in 6 cases (Cases 7, 8, 9, 10, 11, and 12, table 2) in addition to the postero-anterior expiration films. The pneumothorax space was visualized in all views.

TABLE 2

Amount of Pneumothorax Collapse Visualized 24 Hours after Induction

CASE NUMBER	AIR ADMINISTERED	COLLAPSE VISUALIZED IN EXPIRATION
	cc.	*per cent*
1. M. A.	250	25*
2. A. C.	300	20
3. J. B.	200	less than 5†
4. E. T.	250	15*
5. F. K.	250	15
6. M. H.	300	30†
7. E. L.	250	20*
8. R. W.	250	15
9. M. T.	300	10
10. Hy. S.	250	10*
11. S. L.	300	20
12. I. S.	150	10*

* Indicates per cent collapse of upper lobe only.

† Indicates per cent collapse of lower lobe only.

DISCUSSION

As has been noted, in all 12 patients given 150 to 300 cc. of air, a pneumothorax was visualized roentgenographically twenty-four hours later (table 2). With identical technique, but without introduction of air into the pleural space from without, 21 of 23 showed *no* pneumothorax space. If the latter 21 suffered trauma to the lung, it was probably of a degree insufficient to permit leakage of 150 cc. or more of air. The possibility that smaller amounts than this entered the pleural space from the lung cannot be excluded. Roentgenograms in other projections might have shown this, but in 6 cases oblique projections were made and failed to do so.

An alternative explanation is conceivable. It might be argued that, in the cases where air was given, the space visualized twenty-four hours later actually contained more than the amount of air which entered from the outside, possibly lung leakage *plus* the air administered, and that the amount of air necessary for visualization is really much greater than stated. If this were so, perforation of the visceral pleura could have occurred in all of our 23 patients. But for some reason this hypothetical leakage is always less than in the cases where air is given and a space is visualized. Perhaps this is a result of earlier closure of a perforation when

the pleural surfaces are not separated by injected air. On the other hand, it would seem that the injection of air would of itself tend to close a small rupture by decreasing the vacuum in the space.

There is little doubt that lungs which are the seat of very extensive disease are more likely to be traumatized by a pneumothorax needle. Bilateral lesions, emphysema, and contralateral collapse by pneumothorax or thoracoplasty make the hazard still greater. The less diseased portions of the lung are expanding more fully with each inspiration in order to compensate for reduced ventilatory capacity, and it is over these areas that the induction needle is inserted. Furthermore, when a perforation does occur in a lung which contains very extensive fibrosis and emphysema, its closure is impeded by the decreased elasticity of the organ. Most of the cases needled and reported herein were not of this type but were of a character for which pneumothorax is usually used in current practice. In these, the theory that "traumatic induction" is inevitable and unavoidable was not confirmed.

In some instances, despite careful technique, the lung is perforated at induction. This may produce no symptoms. Every patient in whom a space is not demonstrated by manometer readings should have a roentgenogram of the chest in expiration twenty-four hours after needling. A pleural space may be present and may then be visualized because of escape of air through a traumatized visceral pleura.

Further investigation along the lines indicated and using different roentgenographic projections would be helpful in establishing correlation between the amounts of air administered and the roentgenographic appearance following pneumothorax induction.

SUMMARY AND CONCLUSIONS

1. With the method of pneumothorax induction employed, trauma to the lung was proved to have occurred in only 2 of 23 cases. In neither instance were recognizable symptoms noted and the collapse was discovered solely by roentgenography.

2. In 21 of 23 cases it was not possible to demonstrate escape of air from the lung following pleural puncture in amounts sufficient to be seen on expiration radiograms up to twenty-four hours later.

3. A pneumothorax space was invariably demonstrated by identical roentgenographic technique when air in amounts of 150 to 300 cc. was injected.

4. In the majority of patients with unilateral or bilateral moderately advanced pulmonary tuberculosis, the conventional method of pneumothorax induction with a blunt needle does not cause trauma to the lung of sufficient degree to permit escape of air demonstrable by available roentgenographic methods.

SUMARIO Y CONCLUSIONES

Traumatismo Pulmonar en la Inducción del Neumotórax

1. Con la técnica empleada para la inducción del neumotórax, sólo en 2 de 23 casos se comprobó que había ocurrido traumatismo pulmonar. Ni en uno ni en

otro caso hubo síntomas reconocibles y el colapso fué descubierto solamente por la radiografía.

2. En 21 de 23 casos no fué posible observar, después de la punción pleural, escape de aire en cantidades suficientes para mostrarse en las radiografías tomadas a la expiración hasta veinticuatro horas después.

3. Un espacio neumotorácico fué invariablements revelado con una técnica roentgenográfica idéntica al inyectar aire en cantidades de 150 a 300 cc.

4. En la mayoría de los enfermos con tuberculosis pulmonar uni- o bilateral moderadamente avanzada, la técnica convencional de inducción del neumotórax con una aguja roma no ocasiona suficiente traumatismo pulmonar para poder observar escape de aire con las actuales técnicas roentgenográficas.

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A CLINICAL STUDY OF THE TOXIC EFFECTS OF DIHYDROSTREPTOMYCIN AND STREPTOMYCIN[1]

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INTRODUCTION

Dihydrostreptomycin is prepared by the catalytic hydrogenation of streptomycin. It was first described by Peck, Hoffhine, and Folkers (1) in 1946. *In vitro* studies showed that this new drug had about the same antimicrobial spectrum as streptomycin and about the same degree of potency. Subsequent animal and clinical trials suggested that the toxicity might be significantly lower, particularly with respect to "hypersensitivity" reactions and embarrassment of vestibular function (2, 3, 4). More recent studies have yielded conflicting data, some of which seem to show a relatively earlier onset of vestibular damage with streptomycin, but with roughly the same incidence of toxicity with both drugs by the time treatment was concluded (5). Marked hearing loss in as many as 25 per cent of the patients has been reported, occurring two to three weeks after dihydrostreptomycin was discontinued (5). An "explosive" type of vestibular damage has also been seen recently, developing suddenly as early as forty-eight hours after treatment was started with doses presumed to be safe (6).

In most clinical studies with dihydrostreptomycin, the amount of toxicity produced was compared with that which had been produced in the past with equivalent doses of streptomycin. Current opinion about the effect on the vestibular apparatus of two or three grams of streptomycin is based largely on the experience gained from 1945 to 1947, when these doses were widely employed in the treatment of tuberculosis. It was thought desirable to test dihydrostreptomycin against currently produced streptomycin due to the possibility that earlier observations of the toxic effects of large doses of streptomycin might not at present apply.

When the damaging effects of these two drugs are compared in a small series, it is necessary to use a dose high enough to produce a significant amount of toxicity with at least one of the drugs. One gram of streptomycin daily is the usual dose currently employed in the treatment of most forms of tuberculosis. This dose is known to produce vestibular damage in only about 5 per cent of the patients. Thus a very large series of cases would have to be treated with this dose of dihydrostreptomycin before comparable results could be obtained. The alternative method is to treat two groups of patients with dihydrostreptomycin and streptomycin in large enough doses and for a sufficient length of time to produce a significant amount of toxicity in a small series.

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[2] This study was aided in part by a grant from the Division of Research Grants and Fellowships of the National Institutes of Health, Public Health Service. (RG 938 (c), Howard M. Payne, M.D., Principal Investigator).

Early in November 1948 a quantity of dihydrostreptomycin[3] was made available to the Tuberculosis Service at Freedmen's Hospital for toxicity studies. To provide a "control" group, an equivalent amount of streptomycin[4] was obtained. Careful examinations for toxic effects would be carried out at regular intervals.

MATERIALS AND METHODS

Twenty patients were selected for study and were divided into two groups of 10 each in such a manner that age, weight, and sex were roughly the same in both groups. One group was then selected for dihydrostreptomycin treatment, the other to receive equal doses of streptomycin (table 1).

TABLE 1

Comparison of Streptomycin-treated and Dihydrostreptomycin-treated Groups

	TOTAL	STREPTOMYCIN	DIHYDRO-STREPTOMYCIN
Number of patients	19	10	9*
Average age (years)	27.9	27.9	27.9
Average weight (pounds)	121.0	121.0	120.9
Sex:			
Male	6	4	2
Female	13	6	7
Stage of disease:			
Far advanced	14	9	5
Moderately advanced	4	1	3
Minimal	1	0	1
History of streptomycin treatment:			
Within 6 months of study	2	1	1
More than 6 months prior to study	6	5	1

* One patient assigned to the dihydrostreptomycin group died after fifty-seven days of treatment without having shown any signs of toxicity, and is not included in this analysis.

Each patient received 3.0 Gm. of drug daily. This was given in divided doses of 1.0 Gm. every eight hours. Each gram was diluted with distilled water so that each ml. contained 500 mg. The injection was given in the upper outer quadrant of the gluteal region. Because of the large doses of the drug being used, treatment was stopped at the first definite indication of vestibular damage, either subjective or objective, unless the patient's need for and apparent response to treatment justified its continuation.

The toxic symptoms which were a basis for discontinuing either drug were as follows:

1. The syndrome of vestibular dysfunction characterized by:
   a. *Ataxia*—patient unable to walk alone in extreme cases. If they are able to walk, they walk with a broad base and are unable to walk a straight line.
   b. *Nausea and vomiting*
   c. *Visual dysfunction*—initial difficulty in focusing particularly for near vision
   d. *Dizziness*—aggravated by accelerating or turning movements

[3] Obtained from Merck & Company, Inc.

[4] Provided by the Central Coordination and Analysis Office of the Tuberculosis Study Section, National Institutes of Health.

e. *Tinnitus*—ringing, roaring, or hissing sound in either ear
f. *Spontaneous nystagmus*—regular rhythmic movement of the eyeballs in lateral, vertical, or rotary directions with definite fast and slow components
2. Deafness increasing under treatment
3. Severe blood dyscrasias
4. Exfoliative dermatitis.

In addition to the above, pain and local reaction at the site of injection and drug fever were watched for and recorded when they occurred but were not considered as a basis for stopping treatment.

All patients were questioned and examined daily for symptoms and signs of toxicity. Great care was taken to see that no "leading questions" were asked of these patients concerning any of their symptoms, particularly those which might be considered evidence of vestibular damage. No specific questions were asked, for instance, concerning dizziness unless the patient had already volunteered the information that he was dizzy.

Prior to the administration of either drug, determinations of the blood non-protein-nitrogen, complete hemograms, urinalyses, audiograms, caloric stimulation, and roentgenograms of the chest were obtained and were repeated at regular intervals thereafter. One of us has modified the caloric stimulation test devised by Glorig and Fowler (7) in order to make it convenient for large numbers of patients to be tested.

Modified Glorig and Fowler Caloric Stimulation Test

Equipment:
1. Back boards at 30° angle
2. One gallon thermos jug with spigot
3. Rubber tubing
4. Glass tip
5. Centigrade thermometer enclosed in a glass tube so that the water flows past the bulb
6. Floor stands for intravenous administrations
7. Stop watch
8. 20 cc. syringe with short rubber tubing attached
9. Basins, towels, et cetera.

Procedure:
1. The patient is positioned so that he lies on the back rest with the head at an angle of 30° with the floor.
2. The thermos jug is filled with water adjusted to 30° C. and hung from the intravenous stand about eighteen inches above the patient's head. Tubing is connected so that water flows past the thermometer bulb and out the glass tip almost immediately thereafter.
3. The glass tip is introduced into the right external ear canal and the canal is irrigated with water at 30° C. for exactly forty seconds by the stop watch. The duration of the nystagmus produced is then timed from the start of stimulation.
4. If no response is produced, the test is repeated in the left ear.
5. If no response is produced by water at 30° C. in either ear, 20 cc. of ice water (0° C.) is run into the right ear slowly by means of a syringe with rubber tubing tip. The duration of the response is recorded.

Interpretation:
1. If nystagmus lasting longer than 100 seconds is produced by 30° C. in either ear, the response is normal.

2. If no nystagmus is produced by 30° but some nystagmus, however transient, is produced by ice water, the response is diminished.
3. If no nystagmus is produced by either ice water or water at 30° C. the response is absent.

These three categories are mutually exclusive and all test results fall into one of these categories.

TABLE 2

Laboratory Data Obtained on Patients in Both Groups

PATIENT	BLOOD NON-PROTEIN-NITROGEN, MG. PER 100 CC.		URINALYSIS		NEUTROPHIL LYMPHOCYTIC RATIO		LEUKOCYTES PER CU. MM.		EOSINOPHILS PER 100 LEUKOCYTES	
	Before	After	Before	After	Before	After	Before	After	Before	After
S. M.	48	23	Neg.	Neg.	10.5/ 2.8	63.5/33.5	13,700	7,200	0.5	0.0
D. S.	48	22	Neg.	Neg.	60.5/36	69/30	9,200	13,150	3.5	1.0
J. B.	32	25	20 leukocytes per cu. mm.	Neg.	78.5/19.5	67/29	6,650	7,700	1.5	3.0
B. W.	30	26	Neg.	Neg.	58/40	65.5/33.5	5,550	5,000	1.0	1.0
J. M.	51	24	Neg.	Neg.	80/18	70/30	8,850	12,700	0.5	0.0
I. A.	30	23	Neg.	Neg.	82/18	78/21	10,500	13,900	0.0	0.0
R. P.	26	25	Neg.	Neg.	66/29.5	49/31	5,800	4,850	4.5	11.0
R. G.	45	27	30 leukocytes per cu. mm.	Neg.	69.5/26	69/21	6,100	5,000	5.0	5.0
K. P.	44	35	Neg.	Neg.	79.5/	66/31	11,950	9,500	3.0	2.0
L. S.	32	46	Neg.	Neg.	81.5/18	64/34	10,200	7,500	0.0	1.0
M. W.†	48	27*	Neg.	—	82/17.5	—	12,900	—	0.5	—
W. C.	44	39	Neg.	Neg.	67/25	51/34	5,700	5,500	7.0	5.5
F. D.	47	23	Neg.	Neg.	55.5/43	40/52	6,950	5,950	1.0	4.0
G. G.	42	26	Neg.	Neg.	55/41.5	40/54.5	8,300	6,300	2.5	4.0
J. J.	49	26	Neg.	Neg.	74.5/22	58/34	11,650	10,700	2.5	4.0
J. P.	30	28	Neg.	Neg.	71/21	49/31	11,750	6,300	7.0	16.5
U. P.	48	31	Neg.	Neg.	46/53	40/55	4,100	4,600	1.0	2.0
M. R.	34	24	Neg.	Neg.	70/27.5	58/41	7,850	12,150	2.5	1.0
J. S.	43	78	Neg.	Rare RBC per cu. mm.	65/27.5	47.5/49.5	10,100	7,600	5.5	1.0
A. S.	41	21	Neg.	Neg.	67.5/30.5	58/35	7,550	10,650	1.5	5.0

* Obtained during course of treatment

† Patient died

RESULTS

All patients had a normal caloric response, audiogram, concentration non-protein-nitrogen in the blood, and urinalysis prior to starting the treatment. The hemograms were normal in all except 5 in which there was an eosinophilia greater than 4 per cent. Two patients were in the streptomycin-treated group and 3 in the dihydrostreptomycin group (table 2).

The first symptom complained of by all of the patients was soreness at the site of injection which in the majority of cases persisted throughout the treatment. In the dihydrostreptomycin-treated patients, there was a marked diminution in complaints of local soreness and pain when dihydrostreptomycin sulphate was substituted for dihydrostreptomycin hydrochloride. The dihydrostreptomycin hydrochloride was given for the first six weeks of treatment.

Streptomycin Sulfate-treated Group

In the streptomycin sulfate-treated group, no significant symptoms developed until the third week of treatment.

On the fifteenth day of treatment one patient (S. M.) began to complain of severe dizziness, ataxia, visual disturbances, and had spontaneous nystagmus, all of which progressed during the next forty-eight hours. Streptomycin was discontinued on the eighteenth day, after which the symptoms rapidly disappeared. Caloric stimulation tests performed on the tenth, seventeenth, and twenty-fourth days were normal. A caloric stimulation test on the thirty-first day of treatment showed no response to ice water and all tests since that time showed no response.

Another patient (J. B.) developed symptoms on the eighteenth day of treatment lasting for approximately five days. Treatment was not discontinued at this time because the symptoms were considered to have a large subjective component and because the patient's disease seemed to respond favorably to streptomycin. The drug was finally discontinued on the twenty-third day because of increasingly severe vestibular symptoms. A caloric test on the seventeenth day of treatment, just before the onset of symptoms, was normal. Unfortunately, the patient became recalcitrant when her symptoms began and for the next two weeks refused the test. On the thirty-eighth day there was no response to ice water. Since that time weekly tests have shown no response except for a diminished response on three scattered occasions, including the last test which was four months after treatment was started (figure 1).

A third patient (D. S.) developed dizziness and ataxia on the twenty-second day of treatment and the drug was stopped five days later (twenty-seventh day). The caloric response on the twenty-fourth day was normal but there has been no response after the thirty-first day.

A fourth patient (B. W.) experienced transient dizzy sensations on the fourteenth day of treatment which were of short duration and not considered severe enough to justify cessation of treatment. She became ataxic, complained of severe dizziness, and had nausea and vomiting on the twenty-eighth day of treatment. The drug was stopped on the thirtieth day of treatment, after which the symptoms subsided. The caloric stimulation test on the thirty-first day of treatment showed a normal response.

A fifth patient (J. M.) developed symptoms on the twenty-third day of treatment consisting of dizziness, blurred vision, tinnitis, and ataxia. Spontaneous nystagmus was also noted. These symptoms increased in severity until the thirtieth day, at which time the treatment was stopped. A caloric test on the

seventeenth day was normal, but those on the twenty-fourth and thirty-first days were interpreted as showing diminished response. On the thirty-eighth day the test showed no response and all subsequent tests have yielded a similar result.

A sixth patient (I. A.) complained of mild dizziness on the eighteenth day of treatment but her symptoms were not sufficiently severe or characteristic to justify the diagnosis of vestibular damage due to streptomycin. Streptomycin was therefore continued. On the fifty-second day there was progression of her symptoms and a caloric stimulation test showed no response to ice water. Because of this evidence the treatment was discontinued two days later

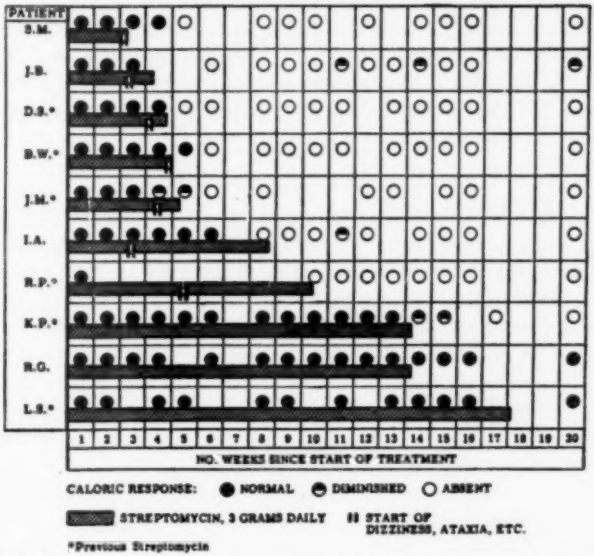

FIG. 1. Relation of symptoms, caloric response and streptomycin treatment (10 patients treated with 3.0 Gm. daily).

(fifty-fourth day). This patient had normal caloric response on the twenty-fourth, thirty-first, and thirty-eighth days during all of which time she was dizzy. The dizziness and unsteadiness of gait which had persisted until the fifty-fourth day rapidly subsided after the drug was stopped. Except for a diminished caloric response on the seventy-third day, all tests since that time have shown no response.

A seventh patient (R. P.) had a normal caloric response at the start of treatment but was considered too ill to be retested until the sixty-sixth day of treatment when a total loss of response was demonstrated and the drug was stopped. This patient complained of dizziness in the third week of treatment persisting as long as the treatment was continued. All the caloric tests after the sixty-sixth day have shown no response.

An eighth patient (K. P.) experienced mild dizziness throughout the ninety days of treatment. At no time was it considered severe enough to indicate vestibular damage. The caloric response throughout treatment was normal. On the fourth and eleventh days after the cessation of treatment, some dizziness was still present and the caloric response was diminished. Eighteen days after the treatment was stopped the caloric response was absent and a follow-up test forty-six days later showed the same result.

The ninth patient (R. G.) was treated for the full three months, receiving a total of 270 Gm. without experiencing any abnormality in caloric stimulation. Seven weeks after cessation of treatment she was still found to have normal caloric response and no specific symptoms or signs of toxicity.

The tenth patient (L. S.) received the full 270 Gm. course of treatment and an additional 96 Gm. immediately thereafter, bringing the total amount received under the study to 366 Gm. He has been completely free of signs and symptoms of toxicity up until the present date. All caloric stimulation tests up to three weeks post treatment were normal.

Dihydrostreptomycin-treated Group

One patient (M. W.) who had far advanced disease died after fifty-seven days of treatment without showing any toxic manifestations. Her death was attributed to pulmonary insufficiency. The remaining 9 patients in this group received ninety days of treatment. None of these showed any abnormality in the caloric stimulation test or experienced any symptoms referable to vestibular damage. When retested seven weeks after the completion of treatment, there was no evidence of vestibular damage.

Although the audiograms showed a slight increase in hearing loss in both groups of patients during the treatment and observation periods, there was no significant difference between the loss in the two groups, and what apparent difference was found can probably be ascribed to the fact that the pretreatment and post-treatment tests were done by two different examiners (table 3). In no case was there as marked a change in the audiogram as has been described by Romansky (5), and all of the patients were able to hear the spoken voice without difficulty.

One patient (J. J.) complained of a roaring tinnitus in the left ear, with its onset four weeks after completing the three-month course of dihydrostreptomycin. Her audiogram two weeks later showed a marked loss at 8,192 cycles in the left ear, but an essentially normal curve through the rest of the audiogram. Twelve weeks after the end of treatment the tinnitus was still present and, although it affected the left ear only, the high-pitch deafness was found to involve the right ear also. There was no significant hearing loss throughout the lower frequencies in the vocal range and, although the patient complained of difficulty in hearing conversation, an interview conducted in almost whispered tones was understood readily. Otoscopic examination was negative.

One patient (J. S.) treated with dihydrostreptomycin showed an increase in from 43 mg. per 100 cc. before treatment to 78 mg. per 100 cc. at the end of

treatment in the blood nonprotein-nitrogen, and red blood cells were present in a catheterized specimen of urine one week after treatment. This patient left the hospital against advice and follow-up was not possible.

TABLE 3

Interpretation of Audiograms

Per cent of "Usable Hearing" Lost During Treatment

	BEFORE TREATMENT	AFTER ONE MONTH OF TREATMENT	SIX WEEKS AFTER CESSATION OF TREATMENT	TWELVE WEEKS AFTER CESSATION OF TREATMENT
Dihydrostreptomycin Group				
W. C.	0.0	0.0	—	—
F. D.	5.6	2.0	0.4	1.2
G. G.	0.1	0.0	—	9.4
J. J.	0.0	0.3	1.5	2.2
J. P.	0.7	1.1	—	10.7
U. P.	0.3	0.0	—	3.5
J. S.	5.1	0.1	—	6.6
A. S.	1.8	0.0	3.8	6.7
M. R.	—	0.4	0.0	0.9
M. W.	1.7	0.8	Died	Died
Average	1.7	0.5	1.4	3.9
Streptomycin Group				
I. A.	0.2	0.3	—	0.6
J. B.	0.0	0.1	—	7.4
R. G.	0.7	0.0	0.6	4.9
S. M.	47.1*	45.5*	6.5*	7.0*
J. M.	2.8	0.1	—	11.6
K. P.	8.6	6.3	—	—
R. P.	1.0	0.3	0.7	0.9
D. S.	0.5	0.7	2.8	1.3
L. S.	1.0	1.1	0.9	1.7
B. W.	3.5	6.8	2.0	5.7
Average	2.0	1.7	1.4	4.3

* Not included in averages

There was also an eosinophilia greater than 4 per cent in 5 patients; 3 patients in the dihydrostreptomycin-treated group and 2 in the streptomycin-treated group. Only one of these patients (R. P.) experienced toxic symptoms (table 2).

This study was not primarily intended for comparison of clinical improvement so that no conclusion as to the clinical efficacy can be made.

DISCUSSION

The high incidence (80 per cent) of vestibular damage among the streptomycin-treated patients is striking when compared with the almost complete absence

of toxicity in the dihydrostreptomycin-traeted group. Although this was a small study, the difference is statistically significant.

In table 1 a comparison is made between the two groups of patients as they were at the time the study was started. Six of the streptomycin group had a history of some previous streptomycin treatment, as compared with 2 in the dihydrostreptomycin group. None of these patients had been treated with more than 20 mg. per Kg. daily, and only 2 (one from each group) had been treated within the six-month period preceding this study. None had shown any signs or symptoms of streptomycin toxicity during or after their previous streptomycin treatment.

The disproportionate number of patients previously treated with streptomycin in the streptomycin-treated group would be grounds for challenge of the comparability of the two groups were it not for the striking difference in the incidence of toxicity found in these two groups during the study. Of the 8 patients in the streptomycin group in whom vestibular damage occurred, 7 developed definite evidence of this damage before the fifth week of treatment and before more than 100 Gm. of streptomycin had been given. Four of these patients had previously been treated with varying amounts of streptomycin (30 to 150 Gm.) but in none of these 4 patients did the total amount of streptomycin received, both prior to and during the study, exceed 200 Gm. before vestibular damage occurred.

Two other patients in the streptomycin group had been given the drug previously. One of these has shown no measurable toxicity. The other (K. P.) had been given 18 Gm. of streptomycin immediately prior to the study at the rate of 1.0 Gm. daily, and showed no definite toxicity until one week after completing the 270 Gm. course of treatment. He was the only example of vestibular damage in the streptomycin group resulting from more than 200 Gm. of streptomycin, whereas all of the 9 patients in the dihydrostreptomycin group tolerated 270 Gm. or more with no measurable vestibular damage whatsoever.

Hinshaw, *et al.* (4) reported that of 14 patients treated with dihydrostreptomycin only 2 showed any evidence of vestibular damage. One of these had developed symptoms of vestibular damage from being treated with streptomycin for twelve days before dihydrostreptomycin was started. The other patient developed what was described as "mild symptoms of vestibular dysfunction" after forty-two days of treatment with 3.0 Gm. per day. Although treatment was discontinued, subsequent caloric tests revealed "moderate hypoactivity of the vestibular apparatus." None of the patients in this series was treated with as large a total dose of dihydrostreptomycin as the patients in our study, although one patient was treated for one hundred and twenty days. The method of testing for caloric response was not described.

Hobson, *et al.* (3) treated 12 patients with dihydrostreptomycin with less striking results. Some of the drug, however, was in a relatively impure form. Seven of these patients were given 5.0 Gm. daily for sixty-five to one hundred and ten days. Of these, 4 showed no caloric response at intervals varying from thirty-three to one hundred and fifty-two days after the beginning of treatment. One patient developed dizziness on the forty-second day of treatment but was treated

for seventy-five days and did not develop an abnormal caloric response until more than one hundred and two days after the start of treatment. Four patients were treated with 3.0 Gm. a day for forty to one hundred days and of these only one was reported as showing an abnormal caloric response, this being a "transient" absence of response on the thirty-second day of treatment. Presumably subsequent calorics were normal. Smaller doses of dihydrostreptomycin for shorter periods of time apparently produced no vestibular damage.

Romansky, Katz, and Glorig (5) have treated parallel groups of patients with 2.0 and 3.0 Gm. per day of dihydrostreptomycin or streptomycin and report that after three months of treatment the incidence of absent caloric response was about equal in both groups, but that the onset of this damage tended to be delayed with dihydrostreptomycin. These investigators used a modification of the Glorig and Fowler caloric stimulation tests similar to that used in the present study. The correlation between absence of caloric response and presence of characteristic symptoms was good in the present study. The team performing the tests was not aware of the symptoms and did not know which drug the patients were receiving. The technique of caloric testing was observed by one of the originators of the test on one occasion and found reliable. We believe it is safe to conclude from the reported observations that administration of a total dose of 270 Gm. of dihydrostreptomycin in ninety days has caused lower incidence of toxicity than would be expected from previously reported studies.

Of the 8 patients in this study who lost their caloric response as a result of being treated with streptomycin, 2 had normal caloric tests at the time treatment was stopped. In another, symptoms of vestibular damage appeared one week before the ninety days of treatment were completed. It was also noted that, when toxic symptoms caused the treatment to be stopped, there was still progression of the damage to a point where there was no response to the stimulation of the semicircular canals. No return of caloric response to normal was observed in any patient during the follow-up period. With the dosage of 3.0 Gm. of streptomycin a day, cessation of treatment does not appear to prevent or minimize the appearance of objective evidence of vestibular damage. None of these patients now appear to be seriously handicapped in the subsequent period of observation.

The lack of damage to the hearing apparatus among both streptomycin and dihydrostreptomycin patients is in marked contrast to the findings of Romansky, Katz, and Glorig (5). With similar doses of dihydrostreptomycin hydrochloride, approximately 20 per cent of their patients showed a marked loss of hearing which progressed several weeks after the end of treatment. In our series no such hearing loss was found, although audiograms were done for twelve weeks after the end of treatment.

In our patients the hydrochloride salt was given for only six weeks, after which the sulfate was used exclusively. Possibly the change to the sulfate forestalled the development of hearing loss, but it is not possible to assume this on the basis of the data available. Further study is needed to clarify the relative toxicities of these two salts of dihydrostreptomycin.

SUMMARY

Ten patients were treated with streptomycin sulfate, 3.0 Gm. per day for a maximum of ninety days, and 9 patients were treated with dihydrostreptomycin, 3.0 Gm. per day for ninety days. All patients were observed daily for toxic manifestations, and weekly tests of caloric response were conducted. None of the patients treated with dihydrostreptomycin showed any signs or symptoms of streptomycin toxicity during the period of treatment or for seven weeks thereafter. Eight of the streptomycin-sulfate-treated patients developed symptoms of vestibular damage and subsequently lost their caloric response, even though treatment was usually stopped shortly after the onset of symptoms. The remaining 2 streptomycin-sulfate-treated patients showed no signs of toxicity in any form. The characteristic signs and symptoms of vestibular damage were always followed or accompanied by complete loss of caloric response whether treatment had been discontinued or not. No significant hearing loss was noted in either group of patients during or after treatment.

CONCLUSIONS

1. The particular lots of dihydrostreptomycin used in this study in a dose of 3.0 Gm. a day given over a period of ninety days were much less toxic to the vestibular apparatus than an equal dose of streptomycin.
2. Discontinuing treatment with 3.0 Gm. doses of streptomycin because of the appearance of vestibular dysfúnction will not prevent its progression.
3. All patients who had lost their response to caloric stimulation showed previous symptoms of vestibular dysfunction.
4. None of the patients showed any significant hearing loss during or after treatment.
5. Further studies are needed to clarify the effect of discontinuing treatment when smaller doses of streptomycin or toxic doses of dihydrostreptomycin are used.
6. Because of the method of selection of patients for this study, it is impossible to come to any conclusions concerning therapeutic effects.
7. Further studies should be done comparing the relative toxicity of dihydrostreptomycin hydrochloride and dihydrostreptomycin sulfate.

SUMARIO

Estudio Clínico de los Efectos Tóxicos de la Dihidroestreptomicina y la Estreptomicina

Diez enfermos fueron tratados con sulfato de estreptomicina, 3.0 Gm. diarios hasta un máximo de noventa días, y otros 9 tratados con dihidroestreptomicina, 3.0 Gm. diarios por noventa días. Todos los pacientes fueron observados diariamente en busca de manifestaciones tóxicas, ejecutándose además pruebas semanales de la reacción calórica. Ninguno de los enfermos tratados con dihidroestreptomicina mostró el menor signo o síntoma de intoxicación estreptomicínica durante el período de tratamiento o por siete semanas después. Ocho de

los tratados con sulfato de estreptomicina revelaron síntomas de lesión vestibular y perdieron después su reacción calórica, aun cuando el tratamiento fué por lo general suspendido poco después de la iniciación de los síntomas. Los otros 2 tratados con sulfato de estreptomicina no revelaron signos de intoxicación en ninguna forma. Los típicos signos y síntomas de lesión vestibular fueron siempre seguidos o acompañados de pérdida total de la reacción calórica, ya se abandonara o no el tratamiento. Ni en uno ni en otro grupo de enfermos notóse pérdida significativa de la audición durante el tratamiento o después.

CONCLUSIONES

1. Los lotes de hidroestreptomicina usados en este estudio a dosis de 3.0 Gm. diarios, administrados durante un período de noventa días, fueron mucho menos tóxicos para el aparato vestibular que una dosis igual de estreptomicina.

2. La suspensión del tratamiento con dosis de 3.0 Gm. de estreptomicina, debido a la aparición de disfunción vestibular, no impedirá la agravación de la última.

3. Todos los pacientes que perdieron su capacidad para reaccionar a la excitación calórica revelaron antes síntomas de disfunción vestibular.

4. Ninguno de los enfermos mostró mayor pérdida de la audición durante el tratamiento o después.

5. Necesítanse más estudios para esclarecer el efecto de la suspensión del tratamiento cuando se usan dosis más pequeñas de estreptomicina o dosis tóxicas de dihidroestreptomicina.

6. Debido al método seguido en la selección de enfermos para este estudio, resulta imposible alcanzar conclusiones relativas a efecto terapéutico.

7. Deben realizarse nuevos estudios comparando la relativa toxicidad del clorhidrato de estreptomicina y del sulfato de dihidroestreptomicina.

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STREPTOMYCIN TREATMENT OF TUBERCULOUS ENTEROCOLITIS[1,2]

Results in 30 Cases

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INTRODUCTION

Streptomycin has been used widely for the control of tuberculous enterocolitis, but published reports are few. Sweany (1) reported on 11 patients in November 1947. Mason, *et al.* (2) reported on 33 patients treated in various Veterans Administration hospitals. There is general agreement among them that streptomycin is unusually effective in relieving symptoms due to tuberculosis of the bowel.

The present study was undertaken for the purpose of determining the results of streptomycin treatment of tuberculous enterocolitis occurring among patients with pulmonary tuberculosis. Various details of the diagnosis, treatment, and results are analyzed and discussed.

PLAN OF INVESTIGATION

The work was done at the Municipal Tuberculosis Sanitarium of Chicago, an institution with 1,300 patients, almost all with pulmonary tuberculosis. The patients reported in this paper are those for whom streptomycin was recommended primarily because of the presence of the gastrointestinal complication. Other patients with gastrointestinal complications, who received streptomycin primarily because of the pulmonary lesions, are not included. Those reported are 30 patients out of a total of approximately 1,000 streptomycin-treated patients. All patients in this group had verified pulmonary tuberculosis, usually far advanced, and all had sputum positive for tubercle bacilli at some time, although in 2 the sputum had become negative prior to streptomycin therapy. There were 19 female and 11 male patients; 21 were white and 9 Negro.

Diagnostic Criteria

The diagnosis of tuberculous enterocolitis was based upon the symptoms, physical examination, course, roentgenographic examination, and proctoscopy. Bacteriological examination of stools was of no value.

Symptoms: The symptoms considered indicative of the disease were: gradually progressive anorexia, nausea, discomfort in the abdomen, pain in the right lower quadrant, and diarrhea. The occurrence of these symptoms, progressing to

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greater severity over a period of several months, was common to most of the patients discussed.

Physical examination: Physical examination usually revealed tenderness, particularly over the right lower quadrant. Thickening of the cecum and gaseous distention of the abdomen were occasionally noted.

Roentgenographic examination: Roentgenographic examinations by means of barium enema were done before, during, and after the course of treatment. The procedure was repeated recently in all patients still available to determine late results. The findings varied considerably. The commonest positive finding consisted of spacticity of the colon, particularly in the cecum and ascending colon, and in some cases irregularity of the mucosa, suggesting ulceration. Shortening and contraction with deformity occurred in some. Double contrast enemas were not used.

Proctoscopic examinations: Proctoscopic examinations were done at intervals; usually the instrument was inserted to a point about 24 cm. above the anus.

Bacteriologic studies: Examination of the stools for tubercle bacilli was done in some cases but was of practically no value in verifying the diagnosis because of the fact that practically all patients in this series were discharging tubercle bacilli in the sputum. Tubercle bacilli can be found in the stools of 30 per cent of patients with pulmonary tuberculosis with no demonstrable gastrointestial disease.

Assignment into groups: On the basis of the diagnostic evidence, the cases were divided into three groups. The first group consisted of 12 patients diagnosed as "verified tuberculous enterocolitis" because of symptoms, physical examination, and course, with or without roentgenographic findings compatible with the disease. In every instance, however, the diagnosis was verified by the finding of tuberculous ulcers on proctoscopy, or the finding of tuberculous lesions on biopsy of the appendix, or by post-mortem findings. The second group consisted of 10 patients diagnosed as "probable tuberculous enterocolitis" on the basis of symptoms, course, and physical examination, usually with bowel roentgenographic findings compatible with this disease. In the opinion of experienced clinicians, there was practically no doubt possible that this group had tuberculous enterocolitis. The third group of 8 patients was diagnosed as "suspect tuberculous enterocolitis" because of symptoms and physical findings suggestive of the disease before therapy. The diagnosis is open to question among the patients in the third group. It is probable that some of these had other causes for their symptoms, particularly functional bowel distress, or they may have had both functional and tuberculous disease. Cases of tuberculous peritonitis are not included in this series.

Therapeutic regimen: All patients were on routine sanatorium rest treatment and received a special nonirritating diet before, during, and after streptomycin treatment. Efforts were made to rule out other gastrointestinal disease by appropriate studies. Many patients had a preliminary course of antiamebic medication as a therapeutic trial. All stools were negative for bacillary dysentery, and no evidence of nonspecific ulcerative colitis was present on proctoscopic examination.

Dosage of streptomycin varied from 0.5 Gm. in one intramuscular injection daily to 2.0 Gm. daily divided into four injections. The duration of treatment varied from forty-five days to several months. The larger dose and longer duration of treatment were used at the beginning of streptomycin treatment in 1947. The majority of the patients received the small dose and short duration of treatment which is still in use.

Observations

In addition to the usual monthly re-examinations of each patient for pulmonary disease, data were collected at intervals on gastrointestinal symptoms, barium enema findings, proctoscopy, stool examinations, and resistance of the microorganisms. All drug-sensitivity tests were performed on tubercle bacilli isolated from the sputum. The follow-up observations were continued to the present time on all patients still alive.

RESULTS

The outstanding features of each case in Groups I and II are shown in tables 1 and 2. The Group III (suspect) cases are not tabulated because of the paucity of objective findings in this group.

Symptoms: In Group I, the "verified" group, 9 (75 per cent) patients showed marked improvement in bowel symptoms, one was unimproved, and 2 died at the end of the course of treatment. In most cases the symptoms were brought under control very quickly, sometimes within a few days, usually within a few weeks. By "marked improvement" is meant great diminution or absence of anorexia, nausea, emesis, abdominal distress, and diarrhea. Gain in weight and improvement in general condition usually followed.

In Group II (10 cases of "probable tuberculous enterocolitis" 4 patients died; 4 (40 per cent) showed marked improvement; 2 (20 per cent) showed slight improvement.

In Group III ("suspect") 4 (50 per cent) patients showed improvement and 4 showed no change.

Of all the patients who showed definite improvement of symptoms on treatment only 3 had recurrence. This was associated with progression of the patients' pulmonary disease several months after the end of treatment.

Physical examination: In the patients who showed symptomatic improvement, there was generally less tenderness over the bowel than prior to therapy. In a number of the patients who achieved good results, there was complete absence of any abnormal tenderness in the cecal region for periods of many months after therapy.

Roentgenographic findings: In the "verified" group, 9 patients showed definite abnormalities on barium enema prior to treatment; of these, 2 died; 5 showed evidence of improvement; and one was unchanged. The evidence of improvement noted usually consisted of lessened spasticity of the colon and less irregularity of the mucous membrane outline. Only one patient with a roentgenogram which revealed pathologic changes before therapy had normal roentgenographic findings after therapy.

In the "probable" group, 6 cases presented definite evidence of bowel abnormalities on barium enema prior to treatment; in 2 cases the barium enema was negative; and 2 patients were too ill for the examination. Barium enema after therapy revealed persistence of pathological findings but some improvement in 4 of the above 6 patients. One patient died, and one revealed progressive improvement to a normal barium enema eleven months after therapy. One patient with normal roentgenogram before therapy presented normal findings after therapy. One patient, normal before, showed contraction and deformity ten months later, associated with relapse in symptoms.

In the "suspect" group, 6 cases showed normal barium enemas before and throughout the observations; 2 revealed minimal evidence of pathology before and after therapy, with no essential change.

Proctoscopic examination: In Group I, 9 patients had single or multiple ulcers prior to therapy; in one case the bowel appeared normal; and in 2 cases proctoscopy was not done.

In Groups II and III, all proctoscopic examinations were negative before and after therapy.

Repeat examinations after therapy revealed healing of all the ulcers except in one patient, in whom some were still present, though smaller two months later. Healing could be noted within a period of weeks. All ulcers remained healed, but in one patient two small (3 mm.) new ulcers were found nine months after therapy.

Biopsy: In 2 cases laparotomy was done for appendicitis and histologic sections revealed tuberculosis.

Post mortems: Two patients died shortly after the end of streptomycin therapy. Post mortems revealed extensive ulcerative colitis in both cases, but no change was observed that could be attributed to streptomycin treatment. These 2 patients (M. D. and L. T.) failed to respond well to streptomycin therapy. Neither had received the drug before. Tubercle bacilli obtained from the sputum were "slightly resistant to 12.5 γ " in one; the other had a negative culture. Symptoms were diminished in one patient while on treatment, unchanged in the other. Both patients had a rapidly progressive course to death. The failure to respond to chemotherapy must be attributed to overwhelming infection in the terminal stage of the disease. There was no evidence to suggest that healing occurred on therapy, with relapse later.

Correlation of Pulmonary and Bowel Improvements in Groups I and II (22 Cases)

In 8 patients whose chest roentgenograms showed definite improvement on streptomycin treatment, improvement of bowel symptoms was also noted. Two of these later showed progression of pulmonary disease with recurrence of bowel symptoms three and twelve months after the end of streptomycin therapy.

Of the group whose chest roentgenograms revealed no definite evidence of improvement, 6 patients died, with slight or no improvement in bowel symptoms; 5 patients had ulcers heal and experienced marked improvement in bowel

TABLE 1

Group I: Verified Cases of Tuberculous Enterocolitis

CASE	TREATMENT	SYMPTOMS		PHYS. EXAM. (ABD.)		PROCTOSCOPIC		BARIUM ENEMA		END RESULT	PULMONARY ROENTGENOGRAM
		Before	After	Before	After	Before	After	Before	After		
1. J. S. M. N. 39 years FAB—Positive	9/11/48 90 days 0.5 Gm. Sens.: SR 100 γ	Appetite poor Distress Diarrhea	Appetite good No pain BM normal	Tender ++	None	12 ulcers 2 to 5 mm. diameter	Completely healed	Narrow spastic cecum and transverse colon	Unchanged	6 months after treatment patient feels improved but has extensive pulmonary tuberculosis + 34 pounds	No change 3 months after treatment
2. M. D. F. W. 18 years FAB—Positive	9/8/47 60 days 1.0 Gm. Sens.: No rept.	Anorexia N&E++ Pain Diarrhea	Same	Tender	Same	Not done Too ill	Too ill	Spasm of cecum	Not repeated	Died after 60 days of treatment. PM revealed extensive ulcers throughout colon	Progressive disease
3. L. T. M. N. 31 years FAC—Positive	9/3/48 60 days 0.5 Gm. Sens.: SR 12.5 γ	Anorexia N&E++ Pain++ Diarrhea	Improved while on therapy. Regressed thereafter	Tender	Same	1 ulcer 4 to 5 mm.	Not repeated. Too ill	Spasm of cecum	Not repeated	Died one month after end of therapy. PM revealed extensive ulcers throughout colon	No change after 60 days of therapy
4. H. W. F. W. 32 years FAB—Positive	6/3/48 120 days 0.5 Gm. Sens.: Culture negative	Pain Diarrhea Appendectomy revealed TB.	Appetite good N&E none No pain BM 1 x day	Tender	None	Normal	Normal	Normal	Normal	Asymptomatic. Thoracoplasty done after streptomycin therapy + 3 pounds	Moderate clearing on therapy. Followed by thoracoplasty
5. J. T F. W. 32 years FAB—Positive	7/4/48 120 days 0.5 Gm. Sens.: SR 100 γ	Cramps Diarrhea 3 to 5 x day	Appetite fair N&E none Pain 0 BM 1 x day	Slight tenderness	Normal	2 ulcers 3 mm.	Healed with scarring. New ulcers present 9 months later	Cecum irregular and spastic	Normal	March 1949 minimal bowel symptoms. Thoracoplasty being done. + 30 pounds	Progressive disease
6. B. F. F. N. 23 years FAB—Positive	8/6/48 120 days 0.5 Gm. Sens.: SR 100 γ	Cramps Diarrhea 2 to 3 x day	Appetite good N&E none Pain 0 BM 1 to 2 x day	Tender	Normal	Several small ulcers	Healed	Normal	Normal	Bowel symptoms absent 90 days after therapy. General condition poor. + 10 pounds	Pulmonary disease progressing

7. E. H. F. N. 21 years FAB—Positive	9/30/48 90 days 0.5 Gm. Sens.: Culture negative	Cramps Diarrhea 10 to 12 x day	Appetite fair N&E none Pain O BM 2 x day Occasional diarrhea	Tender	Normal	1 ulcer 4 mm.	Healed	Spasm of ascending colon	March 1949 Less spasm	Symptoms improved in 2 weeks + 16 pounds	No change in 90 days
8. A. A. M.W. 35 years FAB—Positive	9/17/47 45 days 1.2 Gm. Sens.: No rept.	Anorexia N&E Cramps Occasional diarrhea	Appetite good N&E none Pain O BM 1 x day	Tender mass in RLQ	Normal	Normal	Normal	Normal	Normal	Tuberculous appendix removed. 18 mos. after therapy patient working. Feels well.	No pulmonary lesions seen because of prior thoracoplasty
9. S. M. T. F. N. 21 years FAB—Positive	12/1/48 120 days 0.5 Gm. Sens.: SR 100 γ	Appetite poor N&E Pain Lost 14 pounds	Appetite good N&E none Pain O BM 1 x day	Tender	Normal	Ulcers 2 to 10 mm. diameter	Healed	Spasm and irreg. of cecum	Improved	Bowel symptoms greatly improved General condition not improved.	Progressive disease
10. J. F. M. W. 37 years FAB—Positive	11/20/48 120 days 0.5 Gm. Sens.: SR 100 γ	Anorexia Cramps Diarrhea Wt. loss Fever	Anorexia N&E++ Pain+ BM 2 x day Wt. loss Fever	Tender	Tender large liver (amyloid)	1 ulcer 8 mm.	Healed	Irreg. and spasm of cecum	Marked improvement	Bed patient. Failing	Slight clearing
11. E. H. F. N. 20 years FAB—Positive	1/10/49 120 days 0.5 Gm. Sens.: SR 1.0 γ	Anorexia N&E occas. Cramps Diarrhea 4 to 5 x day	Appetite good N&E none Pain O BM 1 x day	Tender Losing wt.	Normal	Ulcers 2 to 5 mm.	Mostly healed; a few healing March 1949	Deformity of cecum	Considerable improvement	Diarrhea stopped in 2 weeks. + 5 lbs. in 1 month. Thoracoplasty done while on therapy.	Cannot evaluate because of thoracoplasty
12. W. N. M. W. 43 years FAB—Positive	5/13/48 60 days 0.5 Gm. Sens.: Culture negative	Anorexia Cramps Diarrhea 3 to 4 x day	Appetite good N&E none Cramps O	Tender losing wt.	Normal patient has amyloidosis	Several small and one large ulcer	Healed	Spasm and deformity of cecum with ulceration	No spasm	Bowel asymptomatic. General condition stationary. + 9 pounds	Marked clearing

N & E: Nausea and Emesis Sens.: Sensitive bacillus SR: Slight Resistance CR: Complete Resistance PNX: Pneumothorax

TABLE 2

Group II: Probable Cases of Tuberculuous Enterocolitis

CASE	TREATMENT	SYMPTOMS		PHYS. EXAM. (ABD.)		PROCTOSCOPIC		BARIUM ENEMA		END RESULT	PULMONARY ROENTGENOGRAM
		Before	After	Before	After	Before	After	Before	After		
13. W. B. M. N. 40 years FAC—Positive	9/3/48 120 days 0.5 Gm. Sens.: Culture negative (10/1/48) SR 12.5 γ	Anorexia Pain Diarrhea 3 to 4 x day	Slight improvement Died	Tender	Tender Distended	Negative to 24 cm. Fistula in ano	Not re-examined Died	Filling defect in cecum	Marked improvement 2/3/49	Died March 1949. Slight improvement in bowel symptoms.	Progressive disease
14. C. B. F. W. 45 years FAC—Positive	5/26/48 60 days 0.5 Gm. Sens.: CR 100 γ	Anorexia Nausea Pain Diarrhea 8 to 10 x day	Slight improvement	Tender	Tender	Too ill for examination	Died	Not done because too ill	Died	Died March 1949. Slight improvement in bowel symptoms.	No change
15. A. D. F. N. 22 years FAB—Positive	10/4/47 71 days 1.0 Gm. Sens.: No rept.	Anorexia Nausea Emesis Pain Diarrhea	No improvement	Tender Distended	Same	Too ill for examination	Died	Not done Too ill	Died	Died February 1948. No improvement in bowel symptoms	No change
16. C. K. F. W. 43 years FAB—Positive	8/4/47 60 days 1.2 Gm. 11/24/47 49 days 0.5 Gm. Sens.: SR 100 γ (11/4/47)	Anorexia Occasional nausea Pain RLQ	Slight improvement with recurrence later	Cecum palpable	Tender RLQ	Negative to 24 cm.	Negative	Very marked spasm, cecum and asc. colon. Rough irreg. mucosal pattern	March 1949 Deformed but not spastic	Improvement on treatment not maintained. Failing slowly	Moderate clearing followed in 1 year by progression

17. G. K. F. W. 28 years. FAB—Positive	5/15/47 195 days 1.0 Gm. Sens.: No rept.	Anorexia Pain RLQ	Improved No Pain	Tender RLQ	Marked tenderness RLQ	Negative to 24 cm.	Negative	Persistent spasm throughout colon, especially cecum	January 1948 Spastic colon June 1948 Normal March 1949 Normal	Bowel symptoms minimal 22 months after therapy. Chest condition stationary.	Considerable clearing
18. J. McV. M. W. 35 years FAB—Positive	4/24/47 72 days 2.0 Gm. 7/9/47 134 days 1.5 Gm. Sens.: No rept.	Anorexia Nausea Emesis Pain Diarrhea	Appetite good No nausea, emesis or diarrhea	Tender	Slight tenderness RLQ	Negative	Negative	Very marked spasm of ascending colon. Mucosa irregular.	March 1949 Moderate improvement	March 1949 Gained 50 lbs. Eats everything. General condition good. Thoracoplasty done September 1948.	Improved
19. W. S. F. W. 37 years FAB—Positive	7/5/48 65 days 0.5 Gm. Sens.: SR 100 γ	Anorexia Discomfort Diarrhea	Improved but recurred	Tender	Tender, Distended	Negative	Negative	Normal	Normal March 1949	Temporary improvement. March 1949 Anorexia, occasional emesis. BM 1 to 3 x day + 8 pounds Has amyloidosis. Failing.	Improved
20. H. S. F. W. 38 years FAB—Positive	1/6/48 142 days 0.5 Gm. Sens.: No rept.	Anorexia Emesis Pain Diarrhea	No improvement	Tender	Tender	Negative	Died	Ulceration of proximal one-half of colon	Died	Died May 1948	Progression of disease.
21. S. S. F. W. 25 years FAB—Positive	5/18/48 134 days 1.0 Gm. Pre-therapy Sens.: SR 1.5 γ	Nausea Emesis Diarrhea	Spectacular improvement in 5 days	Tender	No tenderness on deep pressure	Negative	Negative	Marked shortening, irregular, and spasm of terminal ileum, asc. and trans. colon	March 1949 Slight improvement	10 months after therapy patient is at home. Appetite good; eats everything except fruits. + 33 pounds BM 1 x day, formed	Marked clearing. Pnx. right and lysis. Extrapl. pnx. left done recently.

TABLE 2—*Concluded*

CASE	TREATMENT	SYMPTOMS		PHYS. EXAM. (ABD.)		PROCTOSCOPIC		BARIUM ENEMA		END RESULT	PULMONARY ROENTGENOGRAM
		Before	After	Before	After	Before	After	Before	After		
22. L. W F. W. 23 years FAB—Positive	5/10/48 121 days 0.5 Gm. Sens.: CR 100 γ (October 1948)	Anorexia Nausea Pain Diarrhea	Improved for 7 months then relapsed 3 months after therapy.	Tender RLQ cecum palp.	Tender RLQ,	Negative	10 months after therapy ulcers noted in rectum	Normal months	10 months after therapy contr. and deform. cecum and asc. colon	3/49—Anorexia, nausea,pain; diarrhea 2 to 3 x day. Lost 16 pounds. Early improvement not maintained.	No improvement

symptoms; and one patient had bowel symptom improvement with recurrence in seven months.

In 2 patients the presence of a thoracoplasty, one done before streptomycin treatment and one after, made evaluation of the pulmonary response difficult. In both cases marked improvement of bowel symptoms occurred.

The best results were obtained in those patients in whom collapse therapy caused the "conversion" of the sputum. Four such patients (3 thoracoplasties and one pneumothorax with lysis) remained asymptomatic three months, nine months, ten months, and eighteen months, respectively, after beginning of streptomycin treatment. Two are at home; one is working (Case 8).

Correlation of Barium Enema with Streptomycin Treatment

Improvement in symptoms was much more marked than improvement in the roentgenographic appearance of the bowel. In patients whose films showed little or no change, it was common to find marked to complete disappearance of symptoms. Improvement, when present in the roentgenogram, usually consisted only of diminution of spasm. All patients who showed improvement roentgenographically also improved symptomatically. Return of an abnormal roentgenogram of the bowel to normal was rare, but was noted in one patient over a period of eleven months. Symptoms in this patient improved rapidly on treatment.

Dose and Duration

The small number of patients allows of no significant statistical analysis of the effectiveness of the various streptomycin regimens. However, the 0.5 Gm., sixty-day course of treatment apparently produced good results in suppressing symptoms and in the duration of this effect. The larger doses and longer courses gave no definite evidence of better results.

Drug Resistance of Microorganisms

Values for the drug resistance of the tubercle bacilli obtained from the sputum at the end of therapy in each case (where available) are indicated in tables 1 and 2. The designation S means sensitive; VSR, very slightly resistant; SR, slightly resistant; and CR, completely resistant. The organisms were cultured on solid medium with 1.0 γ, 10γ, and 100γ of streptomycin per cc. Data are insufficient to determine the effect of resistance on the further clinical course of the enteritis.

DISCUSSION

Prior to the widespread use of collapse therapy, tuberculous enterocolitis was very common, and large numbers of examples were always present in this institution. Collapse therapy procedures have cut down the incidence very markedly in recent years. After the use of streptomycin on a large scale, the incidence was reduced still more, possibly because this complication was prevented either by the drug *per se*, or by the fact that collapse therapy could be used in more patients than before. As a result, the number of cases of tuberculous enteritis

seen recently is very small, and it occurs mostly in patients who already have it when admitted.

It is evident that streptomycin is a most effective drug in the treatment of tuberculous enterocolitis. It usually controls the symptoms quickly, often dramatically. Most patients maintain this symptomatic relief over long periods of time, although several showed relapse in a few months. The latter were patients with progressive pulmonary lesions and sputum positive for tubercle bacilli. Some of the patients seem to remain almost asymptomatic in spite of little or no improvement in the chest roentgenogram or sputum status. In those patients whose disease was progressing rapidly toward a fatal termination, the streptomycin caused little or no improvement in symptoms. The use of narcotics in such patients to control cough, et cetera, tended to cover up the gastrointestinal symptoms, making it difficult to evaluate the effectiveness of streptomycin. In general, streptomycin therapy resulted in rapid disappearance or diminution of anorexia, nausea, emesis, abdominal discomfort, and diarrhea. Often patients became asymptomatic with good appetite and one formed bowel movement daily. They were able to eat almost all foods instead of being restricted to a special bland diet as before. Many were able to eat all the common foods except raw fruits after completion of therapy.

Prior to therapy, the abdomen, and particularly the cecal region, was tender on palpation. After therapy, this sign improved and in some of the patients seemed to disappear. Deep palpation and heavy pressure over the cecum caused no pain in some of the patients examined over a period of months after therapy.

The degree of improvement noted on roentgenographic examination seems slight in comparison with the improvement in symptoms. Although spasm usually disappeared, deformity in the cecal region remained even in the presence of no symptoms and apparently normal bowel function. It may be assumed that superficial ulceration healed and remained healed, as borne out by the clearing of the rectal ulcers. The persistence of deformity suggests deep scarring, but proof of this is still lacking.

Only 2 of the 6 patients who died came to autopsy. The bowel findings of extensive ulceration, worse in the terminal ileum, cecum, and ascending colon, appeared identical with those not treated with streptomycin. These 2 patients had been extremely ill when admitted to the sanatorium and therapy had very slight effect. In one patient diarrhea continued unchecked to the time of death. In the other patient, symptoms improved while on therapy but regressed rapidly after discontinuance; death followed in one month.

No opportunity has presented itself to study the autopsy findings in a patient who had good results from streptomycin therapy of a proved tuberculous ulcerative colitis. It would be of considerable interest to note the anatomical results.

In most cases symptoms of both bowel and pulmonary disease improved together. In a considerable number of cases, however, the improvement of bowel symptoms and objective findings was much greater than the improvement to be noted in the chest roentgenogram. It was relatively easy to obtain bowel improvement with streptomycin, but unusual among these patients to see corre-

spondingly marked objective improvement in the pulmonary picture. It seems to be much more difficult to influence pulmonary than bowel tuberculosis. Whether this difficulty is caused by the relative accessibility of the bowel lesions to the drug by way of the blood stream, or simply reflects the more massive involvement in the lungs, is not evident.

Some of the patients in this series were admitted to the sanatorium with evidence of severe bowel tuberculosis and advanced pulmonary lesions permitting of no collapse therapy. In such patients, as would be anticipated, streptomycin therapy is mainly for symptomatic relief and should be started at once. However, in patients whose general condition is better and who may become candidates for collapse therapy, the timing of streptomycin therapy becomes a matter of importance. From the present experience it would appear advisable to proceed with surgical collapse where indicated, using streptomycin to control the bowel symptoms, in the expectation that a good result will be achieved if sputum "conversion to negative" follows the surgery. In patients being prepared for pulmonary resection it is important to use streptomycin at the proper time. To dissipate its usefulness in treating minor bowel symptoms long before surgery would be unwise.

It is remarkable that reinfection of the bowel mucosa appears to be uncommon after the end of therapy. In most patients, improvement has been maintained over a number of months in spite of sputum positive for tubercle bacilli which would be expected to cause new ulcerations in the bowel. It is not clear whether this failure to reinfect the bowel is due to a diminution in the number of bacilli traversing the bowel after therapy or to some qualitative change in the bacilli. Are resistant strains less likely to cause mucosal lesions; or does the general improvement in the patient's resistance after therapy prevent reinfection? It is evident that the answers to these questions must await a more complete understanding of the mechanism of action of streptomycin.

SUMMARY AND CONCLUSIONS

Studies of 30 patients with tuberculous enterocolitis treated with streptomycin are reported. All had associated pulmonary tuberculosis. Diagnostic criteria, roentgenographic findings, proctoscopic findings, and end results are detailed. Of 12 cases with a "verified" diagnosis, 9 showed marked improvement after treatment with streptomycin. Of all 30 cases, 19 showed improvement. Clinical improvement was usually rapid, often dramatic, and frequently maintained even when a relapse of the pulmonary disease occurred. In 9 cases, rectal ulcers disappeared in 8 immediately after treatment. Change in the status of the roentgenographic findings during treatment did not generally occur.

SUMARIO Y CONCLUSIONES

Estreptomicinoterapia de la Enterocolitis Tuberculosa

Estos estudios comprenden 30 enfermos con enterocolitis tuberculosa tratados con estreptomicina. En todos había tuberculosis pulmonar. Expónense las pautas de diagnóstico, los hallazgos proctoscópicos radiográficos y los resultados ter-

minales. De 12 casos con diagnóstico "comprobado," 9 revelaron decidida mejoría después del tratamiento con estreptomicina. Del total de 30 casos, 19 mejoraron. La mejoría clínica fué por lo general rápida, a menudo dramática, y mantenida frecuentemente a pesar de la recaída de la afección pulmonar. De 9 casos, en 8 las úlceras rectales desaparecieron inmediatamente después del tratamiento. En general, no se alteraron los hallazgos roentgenográficos durante el tratamiento.

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RASMUSSEN'S ANEURYSMS AND FATAL HEMORRHAGE IN PULMONARY TUBERCULOSIS[1, 2]

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INTRODUCTION

One of the most dramatic complications of pulmonary disease is massive hemorrhage. This has been associated, in the minds of most physicians, with pulmonary tuberculosis; and the various aspects of this syndrome have interested many since the early writings of Laennec (1) in 1827. It remained for Fearn (2), however, in 1841 to describe for the first time in some detail the source of a hemorrhage in a patient dying of cavitary pulmonary tuberculosis. He recorded his observations of a ruptured aneurysm within a tuberculous cavity in a patient who died of multiple recurrent pulmonary hemorrhages. The greatest contribution to the consideration of the aneurysmal source of these hemorrhages may be found in the careful and detailed anatomical studies of Rasmussen (3) of Copenhagen in 11 cases published in 1868 and 1869. He described in each of these 11 cases a pulmonary vessel passing through the wall of a tuberculous pulmonary cavity with an aneurysmic dilatation of this vessel into the cavity.

More recently attention has been directed to this subject in papers by Bogen (4), who states that hemorrhage in pulmonary tuberculosis is almost always from a pulmonary artery, and by Auerbach (5), who describes a series of 45 such pulmonary arterial aneurysms in tuberculous patients dying of pulmonary hemorrhage. A variety of other hypotheses have been developed to account for pulmonary hemorrhage in tuberculous patients. Among these are: deficiency of the coagulability of the blood (6); increased permeability of the vessel walls (7); and erosion of pulmonary vessels by enlarged tracheobronchial lymph nodes (8 and 9). This last condition accounts for relatively few cases of hemorrhage in pulmonary tuberculosis, and the exact status of the other conditions has not been clarified satisfactorily. Although most large hemorrhages resulting from rupture of a pulmonic arterial aneurysm occur in cases of pulmonary tuberculosis with cavitation, some occur in patients with primary or metastatic lung neoplasms, bronchiectasis, lung abscess, or other acute or chronic lung inflammations (10).

MATERIAL

From 667 autopsies performed at Dunham Hospital of Hamilton County during the ten-year period 1938–1947, 56 cases were selected in which the patient had either died following a massive pulmonary hemorrhage, or in which an un-

[1] From the Percy Shields Laboratory, Dunham Hospital of Hamilton County, Cincinnati 5, Ohio.

[2] Presented in part at the 1948 session of the Mississippi Valley Conference on Tuberculosis.

ruptured Rasmussen's aneurysm was discovered at autopsy. Forty-nine of these 56 patients died following a massive pulmonary hemorrhage and are the basis for the clinical observations in this study. These 49 cases, with an additional 7 cases in which hemorrhage did not occur but an unruptured aneurysm of a pulmonic artery was discovered as an incidental finding at autopsy, comprise the 56 cases studied for the gross pathological data. Of the 49 patients who died following a massive pulmonary hemorrhage, a Rasmussen's aneurysm was demonstrated in only 29. It is believed, however, that the source of hemorrhage in all of these 49 cases was from such an aneurysm, for Rasmussen stated that he was able to find the source of bleeding in every case after his attention was once directed to the occurrence of these aneurysms. The writers' experience lends some support to this opinion that the more diligent the search, the higher the rate of discovery. Since 1943, when interest in this problem was stimulated at Dunham Hospital, 21 of these aneurysms were found in 26 patients who died as the result of massive pulmonary hemorrhage, while prior to this date only 8 such aneurysms were found in 23 hemorrhage cases. Also only 2 unruptured Rasmussen's aneurysms were found in cases as an incidental finding prior to 1943, whereas 5 have been disclosed since that time.

To a certain extent, the method of preserving and dissecting the lungs as routinely done in this hospital may account for failure to demonstrate the source of some of these hemorrhages. Whenever possible, the lungs and trachea are removed intact from the thorax. The lungs are then inflated with air so that a post-mortem roentgenogram of the lungs alone can be made. The lungs are then distended with 10 per cent formalin until the solution begins to ooze from the pleural surfaces. As will be further demonstrated in the pathological discussion, some of these aneurysms are thin-walled and empty. It is probable that the marked increase in the intracavitary pressure during these procedures may so collapse the aneurysmal sac that it cannot be readily recognized.

INCIDENCE AND ETIOLOGICAL FACTORS

Forty-nine (7.2 per cent) of the 667 patients upon whom autopsy was performed in a ten-year period died as the result of pulmonary hemorrhage. The incidence by sex and color is shown in table 1.

The average age at death for patients dying as the result of hemorrhage is compared with the average age at death for the entire autopsy series in this same period of time in table 2. The ranges of ages of those who died as a result of hemorrhage are as follows: white males 34 to 68 years; Negro males, 22 to 69 years; white females, 19 to 54 years; Negro females, 15 to 45 years. The greatest number of hemorrhages which were fatal occurred between the ages of 30 and 59. No deaths as a result of pulmonary hemorrhage occurred under the age of 21 in males, while in females 4 of the 14 died at 20 years of age or under. In Negro males, there was a ten-year difference between the mean age of the general autopsy population and that of the patients who died as a result of pulmonary hemorrhage, the latter patients dying on the average at an older age. In the other categories, there was no essential difference between the two groups.

Duration of disease: To gain some idea of the relative duration of the disease in patients with massive pulmonary hemorrhage, the average duration of symptoms in months of the various color and sex groups was compared with a control series consisting of 100 consecutive fatal cases of pulmonary tuberculosis which was broken down into similar categories. The results of this comparison are shown in table 3. The average duration of disease for white females was actually 71.7

TABLE 1

Color and Sex Incidence of Fatal Hemorrhage

1938–1947

	FATAL HEMORRHAGE	ALL AUTOPSIES	PER CENT
White Male	21	256	8
Negro male	13	198	6.6
White female	8	96	8
Negro female	7	117	6
Total	49	667	7.2

TABLE 2

Average Age At Death

	FATAL HEMORRHAGE	ALL AUTOPSIES
White male	49.80	48.90
Negro male	42.93	30.40
White female	33.10	35.40
Negro female	26.86	28.00

TABLE 3

Average Duration of Symptoms in Months

	HEMORRHAGE SERIES	CONTROL SERIES
White male	30.25	21.30
Negro male	13.93	14.48
White female	52.50	38.30
Negro female	15.30	10.20

months. In this series, however, was one patient who had had clinically active tuberculosis for twenty-five consecutive years before her death. Since this case weights the average unduly, the average of the remaining cases, 52.5 months, is thought to be more representative of the entire group. In the white race, the duration of disease is about eight to twelve months longer in the group that develops an aneurysm and dies as the result of hemorrhage than in the average case that dies of pulmonary tuberculosis. In Negro males, there is apparently no significant difference in the duration of disease in patients dying of tuberculosis,

whether the complication of aneurysm does or does not arise during the course of the illness. The small number of cases in the series of Negro females, 7, precludes any valid statistical conclusions. There is considerable difference in the duration of the disease when the white patients are compared with the Negro patients. The duration is two to three times longer in the white persons, both in the hemorrhage series and in the average of the autopsy series. This pattern follows the general trend of the difference of the disease in the two racial groups. Similar trends are obtained when the average period of hospitalization of the patients studied here is considered.

TABLE 4

Duration of Symptoms in Months

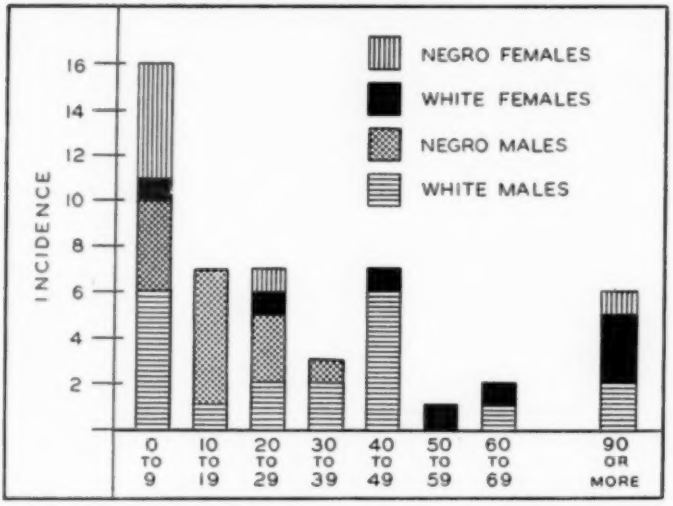

Table 4 presents a graph of the incidence of death in the hemorrhage series as compared with the duration of clinical disease in ten-month periods. In 16 of the 49 cases symptoms considered to be of pulmonary tuberculous origin had been present for nine months or less, while 33, or more than two-thirds of the patients had had similar symptoms for more than ten months. Twenty-six of this latter group had had the onset of their pulmonary tuberculosis at least twenty months before death.

Further evidence of chronicity is found in the fact that in about one-half the cases in this series bilateral and predominantly fibrocaseous tuberculosis was demonstrable in the admission roentgenograms. In 4 of these cases silicosis was also present. In 10 cases the disease was bilateral and predominantly exudative at the time of admission, and in 14 it was unilateral and exudative. The presence of cavity was detected in every case except 2; and in these, although it was not detected clinically or roentgenologically, it was found at autopsy.

Role of syphilis: Since the presence of aneurysms frequently brings up the question of syphilis, this factor was investigated by comparing the incidence of positive serologic tests for syphilis (Hinton and Kahn) in the hemorrhage series with the incidence of positive reactions in all patients coming to autopsy during three consecutive years. In the series of patients dying as a result of massive pulmonary hemorrhage and in those in whom an aneurysm was discovered as an incidental finding at autopsy, the serologic tests for syphilis were positive in 21.8 per cent. In those with a positive reaction, an aneurysm was found in 7 and was not found in 5. In the unselected group from the general autopsy series, the serologic tests for syphilis were positive in 37 of the 175 cases, or in 21.14 per cent. This figure is practically the same as that found for the incidence in the group studied here.

TABLE 5

Hemorrhage prior to Fatal Hemorrhage

None	26
One	7
Multiple	16
1 to 8 years previously	11
4 to 12 months previously	7
Less than 4 months previously	5

DEATH FOLLOWING HEMORRHAGE

Of the 49 patients who died as the result of massive pulmonary hemorrhage, 26, or more than one-half, had no such hemorrhage prior to the one which terminated in death (table 5). Seven patients had one previous hemorrhage, while 16 experienced multiple hemorrhages prior to the fatal one. Of the latter 23 cases, bleeding from the lungs had occurred between one and eight years prior to death in 11; between four and twelve months in an additional 7; while in 5, less than four months elapsed between the time of the first hemorrhage and the time of death.

Of the 49 patients who died as the result of pulmonary hemorrhage, 36 died immediately following this hemorrhage. This latter group includes one case in which the patient survived in a state of shock for a period of eight hours following an isolated hemorrhage. Of this group of 36 cases, 26 had no previous hemorrhage, and death appeared to be due to either blood loss or suffocation. In 3 of these 26, there was no external evidence of hemorrhage at the time of death but evidence of massive bleeding was found at necropsy. Rasmussen (3) commented on the occurrence of such an occult fatal hemorrhage. Others, writing on this subject, have failed to mention either the possibility or the finding of such cases of occult fatal pulmonary hemorrhages. In 10 of the 36 cases, there had been previous hemorrhage over a period varying from three days to three months before the massive hemorrhage which was immediately fatal. Death in these 10 cases also appeared to be due primarily to blood loss or to suffocation; but in a

few, spreading disease as a result of the previous hemorrhages may have been a factor. In 5 cases in which a massive blood loss in the last few hours of life did not occur there were repeated hemorrhages over a period of several days to one year before death. The mode of death in these cases appeared to be due in part to spread of tuberculosis and in part to blood loss. In 8 cases, death followed a single hemorrhage after an interval of four to fourteen days. In these, death was apparently due to spread of an acute tuberculous pneumonia as the result of the hemorrhage. This acute pneumonia may possibly have been on an allergic basis as described by Austrian and Willis (11) who observed the development of "cottony" shadows, roentgenologically, and foci of acute tuberculous pneumonia, pathologically, in the lungs of sensitized rabbits that received intratracheal injections of a mixture of blood and tubercle bacilli. Although in the majority of cases blood loss and obstruction to the trachea and bronchi appeared to be chief factors in the cause of death, in about 25 per cent the development of an acute tuberculous pneumonia may have been the immediate cause of death. Some idea of the unexpectedness of death can be gained from noting that, of the 49 patients who died as a result of massive hemorrhage, 28, or over one-half, were considered well-nourished at the time of death, a state of nutrition unusual in the average patient dying of pulmonary tuberculosis.

PATHOLOGY

A general survey of the lung sections in all 56 cases, including fatalities as a result of hemorrhage as well as cases in which an unruptured aneurysm was found, emphasizes the fact that these aneurysms and the resultant massive hemorrhages tend to occur in the more chronic forms of tuberculosis. Lesions of a fibrocaseous type were described in virtually every protocol of the lung dissection. The sections of the lungs were surveyed, with special attention being directed to those cases in which clinical symptoms referable to tuberculosis had been present for less than ten months. In every case in the entire series, conspicuous foci of pulmonary fibrosis due to tuberculosis were found. Frequently such fibroid or fibrocaseous foci were surrounded by large zones of caseation or monocytic tuberculous pneumonia. In those cases in which the aneurysm was found, such fibrosis was seen in microscopic sections adjacent to the artery of origin of the aneurysm in every instance but one. Microscopically, this one aneurysm did not appear different than the others in the series except for the absence of fibrosis due to tuberculosis around the vessel at the point of origin of the sac. Even in this case, however, with a clinical duration of only four months, numerous fibrocaseous foci were found scattered throughout the extensive masses of caseous and monocytic tuberculous pneumonia (figures 1 and 2).

FIG. 1. (Left) Sagittal section of right lung. A Rasmussen's aneurysm is seen on the posterior aspect of the cavity in the base of the lower lobe. Bronchiectasis and the coarse lacy pattern of diffuse emphysema are apparent.

FIG. 2. (Right) Enlarged view of aneurysm shown in figure 1. Note the tangential course of the vessel of origin to the wall of the cavity. The thickness of the fibrotic wall of the cavity is especially apparent in the basal portion.

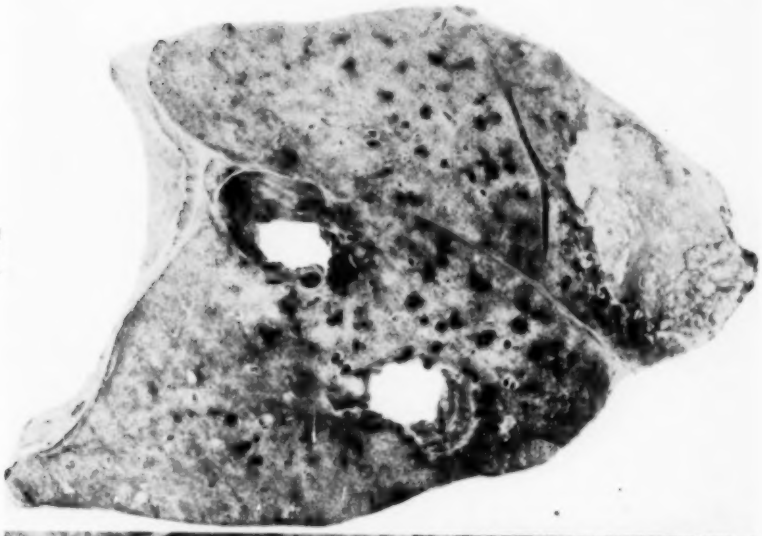

Fig. 1

Fig. 2

Other changes observed histologically were interpreted as indicative of chronic pulmonary disease. Bronchiectasis, most severe in the apical portions of the lungs, was frequently seen. These same zones were also the site of the more marked fibrosis. In addition to dilatation of the bronchi and erosion of the bronchial cartilagenous plates, focal squamous metaplasia of the bronchial epithelium was encountered with moderate frequency. Compensatory emphysema, frequently seen, was usually more marked in the fibrotic parts of the lungs in association with the bronchiectasis; while within the fibrous foci atelectatic alveoli lined with cuboidal cells were common.

Cavity formation was found in every case in this series at autopsy. The cavity containing the aneurysm varied in size from a minimum of 5 mm. to a maximum of 7 cm. in diameter. There was no correlation between the size of the cavity and the incidence of aneurysm formation.

Rasmussen (3) found aneurysms occurred with approximately equal frequency on each side. Auerbach (5) found that aneurysms occurred more frequently in the left lung (26 cases) than in the right lung (19 cases). In this series, single aneurysms were found fourteen times in each lung, while in 6 cases the site of the aneurysm was not recorded. In the other 2 cases aneurysms were found bilaterally; in each, the aneurysm on the right was unruptured while the one on the left was ruptured.

In 21 cases where the site of the aneurysm within the cavity was clearly described, about one-half were found on the medial wall, while the others were located with about equal frequency on the other walls except that none was found on the lateral wall of a cavity.

Intra-arterial injection of radio-opaque material: Using Hill's radio-opaque bismuth suspension (12), arterial injections of 9 sets of lungs were done, using the technique described by Wood and Miller (13). In two instances the bronchial arteries were injected. An aneurysm was found in one case and not in the other. No reference was made to the presence or absence of the contrast medium in a cavity, lumen, in a cavity wall, or in the aneurysmal sac in the case in which the aneurysm was discovered. In the other case the prosector stated that the injection medium was absent within the cavities and that it was not seen in any of the vessels in the cavity walls. The pulmonary arteries of another case were injected with the contrast medium. Gross dissection revealed the presence of an aneurysm but no contrast medium was seen grossly in the lumen of the cavity or the sac, in spite of the fact that the lumen of the vessel of origin was one mm. in diameter. In 6 other cases post-mortem arterial injections of vessels supplying the lungs were done but the protocols fail to mention which vessels were injected. In 3 of these cases an aneurysm was found, while in the other 3 an aneurysm was not identified. Slides of these lungs indicate that post-mortem injection of the pulmonary arteries had been done in 4 of these cases. In one, injection material was found in the lumen of both the aneurysmal sac and the cavity microscopically. Review of the slides in the other 2 cases, in which an aneurysm was not found, suggest that both the pulmonary and the bronchial arteries were injected with contrast medium.

Origin in pulmonary artery: The pulmonary artery was identified on gross dissection as the source of the aneurysm in 7 of the 36 cases in which Rasmussen's aneurysms were found. In 2 additional cases the relatively large diameter of the vessel of origin (4 mm. and 3 mm.) in the mid-portion of the lung where the aneurysms were found point to involvement of the pulmonary rather than of the bronchial arteries. Arterial injection studies indicate that in one case the pulmonary artery was definitely the site of the aneurysm and in another case that it probably was. Thus, in 10 of the 36 cases in which an aneurysm was found, the pulmonary artery was definitely identified as the site of the aneurysm, and in another case the evidence pointed strongly to a similar source. The bronchial artery was not demonstrated as a source of fatal hemorrhage in any case in this series.

Histologic Studies

Histologic studies of 34 aneurysms, 3 of which were examined in serial sections, revealed a picture which was fairly uniform and which varied only in details.

Cavity formation was always present and there was always some evidence of chronicity. Pericavernous fibrosis was always present, but the degree and extent varied considerably. In most cases the fibrosis involved all of the wall as represented in the microscopic sections and usually measured a millimeter or more in thickness. Deep in this zone and lining the cavity was a layer of caseous necrosis with or without an intervening zone of granulation tissue. In several cavities small patches of squamous epithelium were occasionally encountered.

In most of the cases in which the parent vessel could be followed, the course of this vessel was almost tangential to the wall of the cavity. As the vessel approached the wall of the cavity it passed through a zone of diseased pulmonary tissue and usually started to dilate slightly. Concomitantly, a variable degree of endothelial thickening usually occurred so that the lumen of the vessel was slightly constricted (figure 3). Similar obliterative endothelial changes were observed in the other large vessels in the vicinity of the cavity wall. In those other vessels which did not give rise to aneurysms and which actually encroached on the vomica, however, the obliteration of the lumen was complete. Serial sections revealed that the vessel wall proper dilated eccentrically, the dilatation taking place only on the side towards the lumen of the cavity. Finally a point of rupture of the media was encountered. At this point the walls of the media retracted quickly or were reflected back on themselves at an acute angle (figure 4). Through this defect the thickened endothelium protruded and formed the lining of the sac (figure 5). Fibrinoid changes, emphasized by Auerbach (5), were usually seen in the ruptured aneurysms and were frequently seen in the unruptured ones. This change usually started in the thickened endothelium at a point where the vessel wall was intact and it increased in thickness as it slowly spread over the lining of the vessel, usually forming a conspicuous part of the wall of the aneurysm near the neck of the sac (figure 6). Surrounding the endothelial layer, with or without the associated fibrinoid changes, was a relatively thick wall near the junction of the aneurysmal sac with the vessel. This wall usually contained a

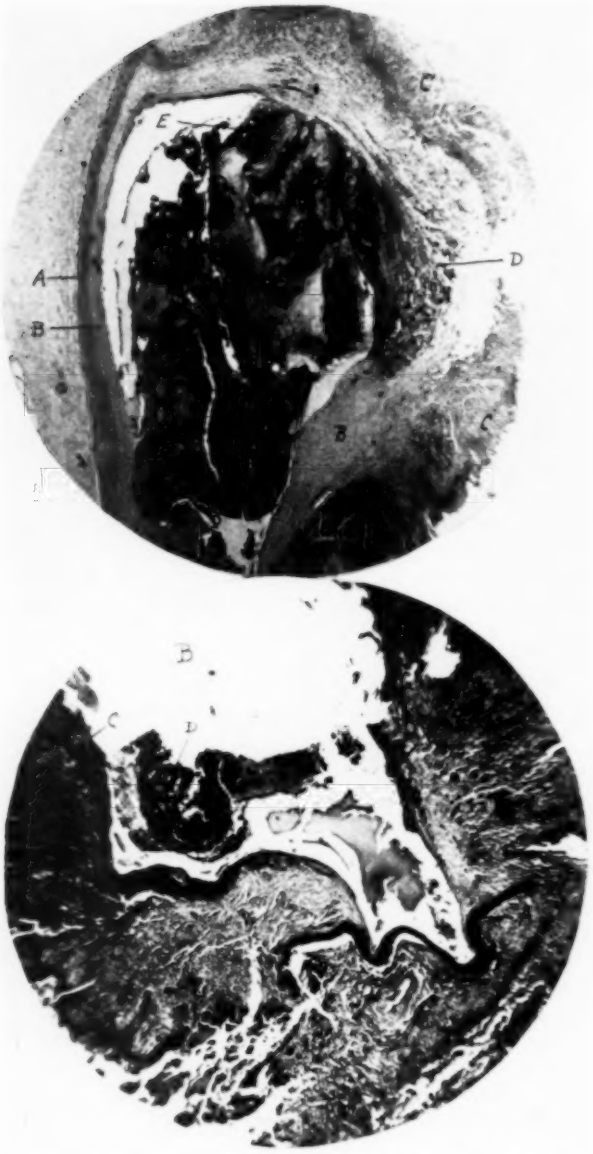

FIG. 3. (Top) Microscopic section of aneurysm shown in figures 1 and 2. A, media of artery; B, thickened layer of endothelium; C, caseous necrosis lining cavity and covering aneurysm; D, fibrinoid degeneration; E, fibrin clot.

FIG. 4. (Bottom) Microscopic section showing reflection of ruptured media. A, media of artery; B, lumen of aneurysm; C, fibrinoid degeneration; D, fibrin clot.

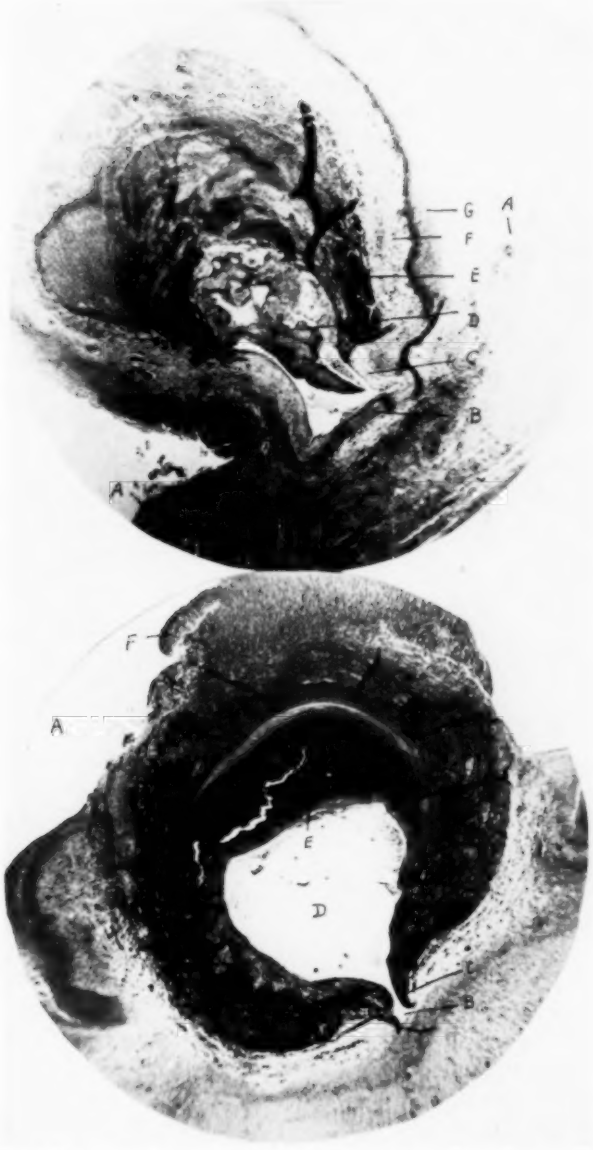

FIG. 5. (Top) Unruptured aneurysm. A, cavity wall; B, media of artery; C, thickened endothelium; D, fibrin clot; E, fibrinoid degeneration; F, granulation tissue; G, caseous necrosis.

FIG. 6. (Bottom) Unruptured aneurysm. A, lumen of cavity; B, vessel of origin; C, thickened endothelium with fibrinoid degeneration; D, lumen of aneurysm; E, fibrin clot; F, caseous necrosis.

conspicuous amount of collagenous tissue. Occasionally a part of the wall of the aneurysm at this point was composed of granulation tissue in which were numerous, dilated, thin-walled blood vessels. In several instances this granulation tissue zone composed the bulk of the wall of the aneurysm, extending from the zone of fibrinoid degeneration outward. The combination of these two processes, fibrinoid degeneration and formation of granulation tissue, thus removed all trace of the preceding endothelial change. The most superficial layer of the aneurysm was usually a thin zone of caseous necrotic tissue.

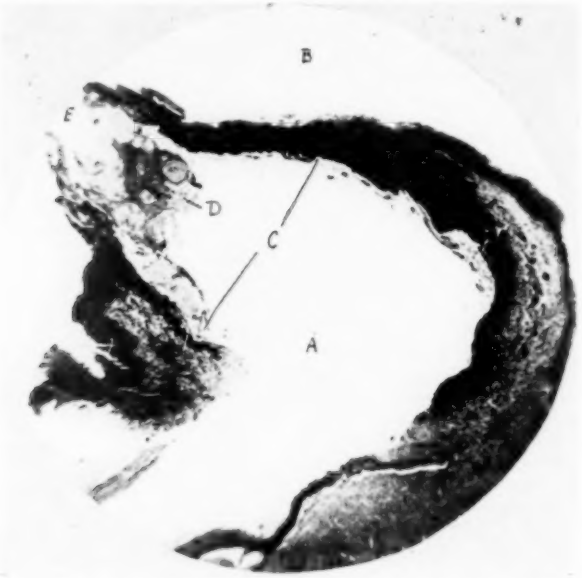

FIG. 7. Ruptured aneurysm. Note the small amount of fibrin present in the aneurysm sac. A, lumen of aneurysm; B, lumen of cavity; C, walls of aneurysm; D, fibrin clot; E, point of rupture.

Within the sac, laminated layers of fibrin were usually seen. These were usually scanty near the neck of the sac and more numerous and denser in the upper portion. This mass of fibrin was always seen in the unruptured aneurysms and it was usually present in the ruptured ones. In several patients dying of massive terminal hemorrhage, however, this mass of fibrin was absent (figure 7).

DISCUSSION

It has been repeatedly emphasized in the past that the development of Rasmussen's aneurysms and the resultant massive hemorrhages tend to occur in the more chronic forms of cavitary pulmonary tuberculosis (3, 4, 5, 14, and 15). Support for this concept is seen in the fact that these patients in general tended to have a longer duration of their disease than the average patient who died of tuberculosis, and the disease was predominantly fibrocaseous in admission

roentgenograms. Thirty-three of the 49 who died of hemorrhage had clinical symptoms referable to pulmonary tuberculosis for ten months or more before the fatal hemorrhage. All of these 33 cases were diagnosed as having fibrocaseous pulmonary tuberculosis at autopsy. Of the 16 patients who had clinical symptoms of pulmonary tuberculosis for nine months or less, and who subsequently died as a result of a massive pulmonary hemorrhage, all but 2 had fibroid or fibrocaseous disease histologically. In these 2, with duration of symptoms of five and seven months, the disease was chiefly exudative with only small foci exhibiting early signs of organization. Further pathological evidence of chronicity was seen in the foci of squamous epithelium lining some cavities, the pericavernous atelectasis and cuboidal metaplasia of the alveolar linings, saccular or cylindrical bronchiectasis, and the focal or extensive obliterative pleural fibrosis.

In addition to evidence of chronicity in the series of aneurysms, another noteworthy pathological feature is the fact that in all cases where the course of the vessel into the aneurysm could be traced, this course was tangential to the wall of the cavity. The artery therefore approaches the cavity through a relatively thick zone of fibrotic scar tissue which may interfere with the circulation in the vasa vasorum derived from the bronchial arteries (16) which are the nutritional vessels for the pulmonary arteries. In addition, intimal proliferation increases the thickness of the wall and adds to the problem of the supply of nutrition to the wall. Thus, when a portion of the wall is finally involved focally by a tuberculous process, the defense mechanism is inadequate, the wall is weakened, and focal dilatation occurs, with the formation of an aneurysm. In addition to the focal involvement of the wall of the vessel because of its tangential approach to the cavity, the loss of normal support in this same area aids in the formation of the aneurysm.

The fibrous encapsulation of the vessel of origin, in addition to aiding in the formation of the aneurysm, may also play a part in permitting massive hemorrhage to occur. A vessel encased in such rigid fibrotic tissue is less able to contract sufficiently to diminish effectively or to stop the bleeding.

One factor exists, however, which may temporarily or permanently stop the bleeding. This is the fibrin clot (3 and 5) which is formed in the sac as the aneurysm develops. Such a fibrin clot is seen in every unruptured aneurysm and absent in many of the ruptured aneurysms. The 23 cases in this series which had one or more fatal hemorrhages prior to the fatal one support Rasmussen's theory that this fibrin clot may occasionally plug the rent in the aneurysmal sac and thus stop the hemorrhage for a variable period. If the fibrin clot is completely extruded, however, a valuable defense against fatal hemorrhage is lost. Even if this valuable defense is lost, other factors may control the bleeding: reduction of pressure and rate of flow in the pulmonary circuit; the tamponade effect of blood accumulating; and occasionally the clotting of the blood in the cavity and communicating bronchi.

Such clot formation in the bronchi has been dramatically demonstrated by Wilson (17) in a case with massive pulmonary hemorrhage. Spontaneous cessation of the hemorrhage was followed in three days by signs and roentgenographic evidence of massive atelectasis of the right lung. Four days later the patient

coughed up two large bronchial blood casts, after which the atelectasis cleared and the lungs returned to their previous status. After eight more months of bed rest, the patient's tuberculosis was considered arrested. Jackson and Diamond (10) have reported a similar occurrence in hemorrhage of nontuberculous origin.

Rasmussen noted the occurrence of occult hemorrhage as a cause of death. Likewise, in 3 cases in this series the patients who had had no previous hemorrhage were found dead in bed unexpectedly. On external examination there was no obvious explanation for death. At necropsy large quantities of blood were found in the lungs and bronchi. At least four different factors may have been instrumental in producing death in such a fashion: (a) suffocation from sudden aspiration of blood and obstruction of the bronchi; (b) debilitation of sufficient degree that the effective clearing of the bronchi by coughing could not take place; (c) reflex laryngeal spasm from foreign material (blood) in the bronchi and trachea; and (d) cerebral anoxemia. Sudden massive pulmonary hemorrhage may result in reduction in the pressure of the lesser circuit, just as shock develops from hemorrhage from the systemic circulation. This drop in pressure would lead to a reduced return of blood to the left side of the heart with resulting forward cardiac failure and inadequate blood flow to the brain. One or more of these factors may well play a part in the mechanism of death in any of the 36 cases in this series in which death occurred immediately after a massive pulmonary hemorrhage.

SUMMARY

1. A series of 56 cases is presented, in 49 of which death occurred as a result of massive pulmonary hemorrhage. These cases represent 7.2 per cent of 667 autopsies performed during a ten-year period. The source of this hemorrhage was identified as a Rasmussen's aneurysm in 29 cases and a similar source of hemorrhage is postulated from the remainder. In 7 other cases an unruptured Rasmussen's aneurysm was discovered as an incidental finding at autopsy.

2. Aneurysms and fatal pulmonary hemorrhage tend to occur more frequently in cases with a more chronic type of tuberculosis, both clinically and pathologically. Age, sex, race, and the presence of syphilis have no apparent significance in the development of these aneurysms.

3. A branch of the pulmonary artery could be identified as the site for the formation of the aneurysms in 11 cases. About one-half of the aneurysms which were located occurred on the medial wall of the cavity.

4. Perivascular fibrosis is discussed as a factor in the pathogenesis of Rasmussen's aneurysms and as a handicap to the control of bleeding from such an aneurysm.

5. Some of the factors contributing to death as a result of pulmonary hemorrhage are discussed.

SUMARIO

Aneurismas de Rasmussen y Hemorragia Letal en la Tuberculosis Pulmonar

1. En 49 de los 56 casos de la serie presentada, la muerte sobrevino a consecuencia de hemorragia pulmonar masiva. Esos casos representan 7.2 por ciento

de 667 autopsias ejecutadas durante un decenio. La causa de la hemorragia fué identificada como aneurisma de Rasmussen en 29 casos y presúmese que fué semejante en los demás. En otros 7 casos, se descubrió fortuitamente en la autopsia un aneurisma de Rasmussen intacto.

2. Los aneurismas y la hemorragia pulmonares letales suelen ocurrir más frecuentemente en los casos con la forma más crónica, tanto clínica como patológicamente, de la tuberculosis. La edad, sexo, raza y presencia de sífilis no guardan aparentemente relación con la formación de esos aneurismas.

3. En 11 casos pudo identificarse una rama de la arteria pulmonar como asiento para la formación del aneurisma. Aproximadamente la mitad de los aneurismas localizados quedaban en la porción media de la pared de la caverna.

5. La fibrosis perivascular es discutida como factor en la patogenia de los aneurismas de Rasmussen y como obstáculo al tratar de cohibir la hemorragia procedente de unos de esos aneurismas.

6. Repásanse algunos de los factores que contribuyen a la muerte debida a una neumorragia.

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TUBERCULOSIS OF THE TRACHEA AND MAJOR BRONCHI[1, 2, 3, 4]

OSCAR AUERBACH

(Received for publication May 4, 1949)

INTRODUCTION

In 1937 at a symposium upon inflammatory diseases of the bronchi, in which the writer (1) was one of the participants, great stress was laid upon the high frequency of clinically demonstrable tuberculosis of the trachea and major bronchi. This appeared to be at variance with our autopsy experience.

In an effort to evaluate the pathologic anatomy of the disease it was decided to study the trachea and major bronchi in 1,000 consecutive autopsies on tuberculous patients. Where gross lesions were present, sections were taken for microscopic study. In the absence of gross lesions, routine sections were taken from the posterior wall of the trachea and major bronchi.

COMPOSITION OF SERIES

Incidence: In 421 cases (42.1 per cent) there was evidence of tracheobronchial tuberculosis; 222 of these showed gross ulceration, 187 showed only microscopic evidence of tuberculosis, while in 12 it was secondary to a rupture of a regional lymph node into the tracheobronchial tree.

Age: The age distribution (table 1) parallels very closely that in the general autopsy series. This is readily explained by the fact that the greatest number of cases in the general series died of chronic pulmonary tuberculosis, of which tracheobronchial tuberculosis in most instances is a complication.

Sex: There were 266 (63.2 per cent) men in this group and 155 (36.8 per cent) women. This compares with 71.5 per cent men and 28.5 per cent women in the general autopsy series. Thus it would appear that tracheobronchial tuberculosis tends to develop a little more frequently in female than in male patients with tuberculosis.

Color: White individuals were affected 234 times (55.7 per cent), Negroes 183 times (43.4 per cent), and Asiatics four times (0.9 per cent). The general autopsy series shows 61.3 per cent whites, 37.6 per cent Negroes, and 1.1 per cent Asiatics. The greater incidence in Negroes may be attributed to a difference of the pulmo-

[1] From the Laboratory Service, Halloran Veterans Administration Hospital, Staten Island, New York.

[2] Presented before the Medical Section, as part of the symposium on *Streptomycin and Extrapulmonary Tuberculosis*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 4, 1949.

[3] Sponsored by the Veterans Administration and published with approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

[4] This material was gathered while the author was at Sea View Hospital, Staten Island, New York.

nary disease, which is frequently a more acute process among that race. Here there is a greater likelihood of spread to the intestine and tracheobronchial tree.

Associated pulmonary tuberculosis: Chronic pulmonary tuberculosis was present in 405 instances in this series. In 4 cases the lungs showed an acute miliary tuberculosis without any evidence of cavities in the lungs. The miliary foci in the tracheobronchial tree and those in the lungs in these 4 cases were part of a generalized miliary tuberculosis from an extrapulmonary focus. In 12 cases there was no evidence of tuberculosis in the lungs before the rupture of a caseous lymph node into the tracheobronchial tree.

Duration of chronic pulmonary tuberculosis: The duration of illness (table 2) was calculated on the length of time during which the patient's sputum was positive for acid-fast bacilli. In the 405 cases of chronic pulmonary tuberculosis, 159 (39.2 per cent) had a duration of from one to twelve months, 70 (17.3 per cent) from thirteen to eighteen months and 48 (11.9 per cent) from nineteen to

TABLE 1

Age

Age in years.....	1 to 10	11 to 20	21 to 30	31 to 40	41 to 50	51 to 60	60 and over
Cases.....	4	51	111	117	65	47	16

TABLE 2

Duration of Chronic Pulmonary Tuberculosis

Months	Up to 12	13 to 18	19 to 24	25 to 30	31 to 36	37 to 42	43+
Cases.....	159	70	48	22	22	3	81

twenty-four months. In 128 (31.6 per cent) cases the pulmonary disease was present for two years or more.

Associated "tract tuberculosis"[5]*:* In 218 (51.8 per cent) cases in this series there was a concomitant involvement of the larynx, intestinal tract, and the tracheobronchial tree. In 127 (30.1 per cent) instances the tracheobronchial tree and the intestines were affected. In only 63 (14.9 per cent) of the cases in this series was the involvement limited to the trachea and major bronchi. In 13 (3.2 per cent) of the cases the "tract tuberculosis" was limited to the larynx and the tracheobronchial tree.

It is of interest that tracheobronchial tuberculosis is part of a tendency toward the development of "tract tuberculosis" in the great majority of cases (85 per cent). In the large majority of cases in this series the tuberculous process in the various tracts was a rapidly progressing one and was associated with an advancing chronic pulmonary tuberculosis.

PATHOLOGIC FINDINGS

Distribution: The type and distribution of lesions (table 3) reveals an interesting contrast when the gross and microscopic findings are compared. A survey of

[5] In the interests of simplicity, the term "tract tuberculosis" is used in this paper to designate involvement of the laryngeal and gastrointestinal tracts.

TABLE 3

Distribution of Tracheobronchial Tuberculosis and Relation to Pulmonary Cavitation in 405 Cases of Chronic Pulmonary Tuberculosis

EXTENT OF TRACHEO-BRONCHIAL INVOLVEMENT	TRACHEA AND BOTH MAJOR BRONCHI			TRACHEA AND RIGHT MAJOR BRONCHUS			TRACHEA AND LEFT MAJOR BRONCHUS			TRACHEA ONLY			RIGHT MAJOR BRONCHUS			LEFT MAJOR BRONCHUS			RIGHT AND LEFT MAJOR BRONCHUS		
	Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total
Bilateral cavitation	45	7	52	40	13	53	20	9	29	42	33	75	3	29	32	5	32	37	0	8	8
Unilateral cavitation	20	0	20	16	4	20	8	4	12	5	12	17	10	13	23	8	15	23	0	4	4
Total	65	7	72	56	17	73	28	13	41	47	45	92	13	40	55	13	47	60	0	12	12

the cases of gross ulceration shows only 26 cases in which the ulcers were found limited to either of the major bronchi. The trachea alone, or in combination with either or both major bronchi, contained ulcers in the remaining 196 cases. In those cases where the tracheal ulceration was present in association with bronchial ulceration, the ulcers in the trachea in some instances were either of the same anatomic age as those in the bronchus or even older. In these cases the ulcers were usually separated by intact mucous membrane. More often, however, the ulcers were more numerous and older in the bronchus than in the trachea and the tracheal ulceration was limited to the corynal region. Very often where the ulceration was present in the three segments there was extensive involvement of one major bronchus, while the tuberculous ulcers were limited to the inferior portion of the trachea and superior part of the opposite major bronchus. In the latter instances the progressive decrease in intensity of the process spoke for an extension from the greatly involved bronchus to the trachea and then on to the opposite major bronchus. This appeared to be the case in almost all of the 149 instances where the trachea and major bronchi were involved by the ulcerative process.

The presence of extensive ulceration in the trachea and major bronchi was invariably associated with an extensive and progressive pulmonary tuberculosis in which there was also an extensive tuberculous involvement of the intestinal tract and of the larynx.

Relationship of site of cavities to tracheobronchial ulceration: In each of the 222 cases with grossly evident ulcers, cavities were present in the lungs. It is noteworthy that in all cases where only one major bronchus was involved the cavities were always present on the same side. In those cases where bilateral cavitation was present, the greatest bronchial involvement was usually on the side of the older cavities.

The foci which were first discovered on microscopic examination were almost evenly distributed among the trachea and major bronchi. However, the presence of foci in two segments of the tracheobronchial tree was noted in a much less proportion than in the group with ulcerations.

Location: The classic ulcer may occur in any portion of the wall but shows a predilection for development on its posterior surface, then the lateral portion, and least frequently in the anterior aspects.

The ulcers may develop at any level in the tracheobronchial tree but show a definite tendency to develop at the coryna. In many instances the tuberculous process is limited to the posterior wall of the corynal region. In occasional cases (three in this series) the tuberculous process was limited to the upper part of the trachea in its entire circumference. These were cases in which there was a direct progression from an extensive laryngeal tuberculosis.

Gross appearance: The size of the ulcers in this series varied from 1.0 mm. to 3.0 cm. The great majority of ulcers are from 1.0 to 5.0 mm. in size. Their long axes are parallel to the cartilaginous rings and they are lined by a yellow granular zone. Very often the intervening mucous membrane between the ulcers has a brown granular appearance. In this early stage the ulcers are usually present in the inferior aspect of the trachea or the superior aspect of a major bronchus on

the posterior wall. The presence of recent superficial ulcers of about the same anatomic age along the greater part of the trachea and major bronchi in some of the rapidly fatal cases speaks for a simultaneous infection of the tracheobronchial tree in these instances.

As the process continues, the ulcers increase in size and number. The ulcers appear in increasing number and first extend along the posterior wall. When the process begins in a major bronchus, the ulcers progress inferiorly and superiorly. In this latter extension it continues into the trachea and on to the superior por-

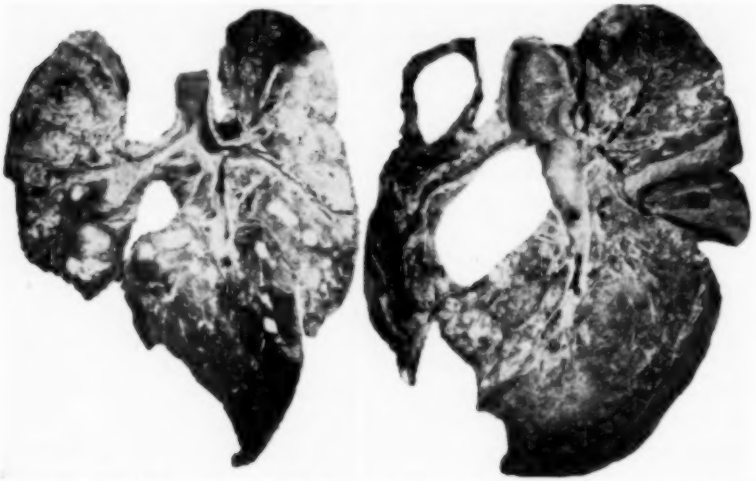

FIG. 1. (Bronchial stenosis I). (Left) Coronal section of the lungs of a 35-year-old woman who had chronic pulmonary tuberculosis for three years. There is a stenosis of the left major bronchus. The compressed lung is occupied almost exclusively by cavities and areas of caseous lobular pneumonia.

FIG. 2. (Bronchial Stenosis). (Right) Coronal section of the lungs of a 51-year-old man who had chronic pulmonary tuberculosis for three and one-half years. The lumen of the stenotic left major bronchus measures 5 mm. in diameter. The corresponding compressed lung contains a large cavity in the upper lobe, a slit-like cavity in the lower lobe.

tion of the opposite major bronchus. Progression of the tuberculous ulcers originating in the tracheal wall will be inferiorly toward a major bronchus and superiorly toward the larynx. With the enlargement and increase in number of the ulcers, fusion frequently occurs. In the far advanced cases only remnants of intact mucous membrane lie between the communicating ulcers.

In most instances the ulcers are superficial and cause no thickening of the wall of the tracheobronchial tree. Most of the cases of ulceration in this series are associated with a rapidly progressing chronic pulmonary tuberculosis and are of a relatively recent origin. An occasional case shows evidence of chronic ulceration, manifested by the presence of single or multiple, thick-walled ulcers usually

located on the posterior and lateral wall. The lumen of the tracheobronchial tree over these thickened ulcers becomes somewhat narrowed and somewhat distorted. In rare instances the cartilage may lie partially exposed at the base of the ulcer.

Occasionally, the ulcerative process and the healing changes within the wall may be so extensive that they cause a marked narrowing of the lumen. In these cases the wall of the bronchus is thickened from 5.0 mm. to 1.0 cm. and the normal architecture is completely distorted by firm, grey, fibrous tissue. The

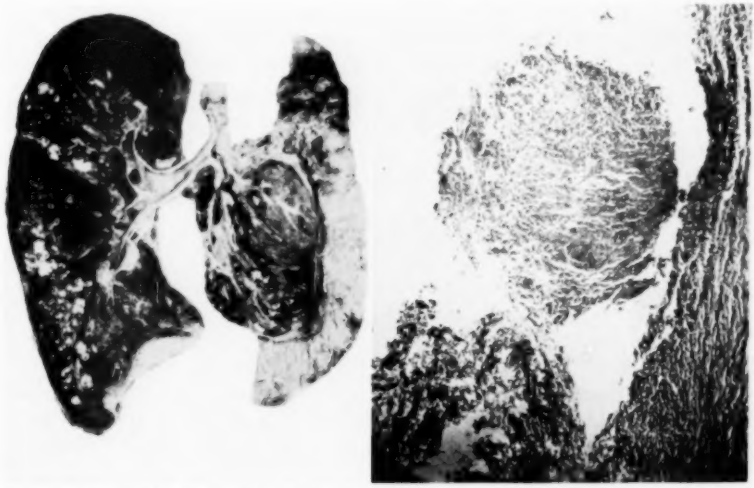

FIG. 3a. (Bronchial Stenosis). (Left) Coronal section of a 26-year-old woman who ha chronic pulmonary tuberculosis for two years. The lumen of the stenotic right major bron chus measures one mm. in diameter. Caseous particles lie in the lumen of the bronchus The circumference of the trachea is greatly narrowed as a result of healing of an extensive tuberculous process within it. The compressed right lung contains encapsulated caseous calcified foci chiefly in the lower lobe. There are no cavities in either lung.

FIG. 3b. (Right) Photomicrograph of the caseous mass and the wall of the bronchus (figure 3a). The caseous nidus lies free in the lumen. The inner wall of the involved bronchus is composed of granulation tissue and the outer aspect by hyalinized connective tissue.

lumen is narrowed from 2.0 to 10 mm. in diameter and the stenosed bronchus is completely ulcerated. Large, irregular, caseous masses attached to the inner wall in one of the cases further narrowed the lumen of the bronchus (figure 3a).

Microscopic appearance: The evolution and the development of the tuberculous process in the trachea and bronchi are similar to these processes in the larynx and the gastrointestinal tract. The first changes are due to the presence of small oval and round foci within the wall. The size and number of these foci varies with the individual cases. The number varies from a single focus present in one of the three structures examined to many foci in all microscopic tissues examined. Most of the foci are located in the immediate subepithelial portion of the wall and in

the region of the mucous glands. In the more advanced process the foci are also present in the adventitial portions. Occasionally the foci within the wall are found only in the adventitia.

The foci in most instances are small and are typical epithelioid giant cell tubercles, with or without a central zone of caseation. The larger foci usually have a caseous center. In the great majority of instances the foci show no tendency towards progression but go on towards anatomic healing.

The development of the ulcer occurs in two ways from the enlargement of a subepithelial focus. First, the focus as it enlarges may cause a pressure atrophy of the overlying epithelium and when this is complete the focus may then rupture into the lumen and an ulcer is thus formed lined by an inner caseous wall. Second, a large caseous focus develops in the submucosa adjacent to the epithelium and in its progression envelops the mucosa in the caseous process. The caseous focus undergoes liquefaction and after pouring its contents into the lumen forms an ulcer lined by caseation.

Since the foci which develop into ulcers are small, the resultant ulcers are small also. A narrow zone of tuberculous vascular granulation tissue surrounds the inner zone of caseation. The caseous lining is replaced by a pyogenic membrane formed by the fibrin exuded from the capillaries of the vascular granulation tissue. The zone of granulation tissue is usually narrow and only occasional foci are present beyond it, thus accounting for the lack of thickening and distortion observed in the region of the wall of the ulcers.

In the later stages the foci beyond the zone of granulation tissue rupture into the lumen and the area of granulation tissue forming the wall of the ulcer widens. In a continuing process of progression and healing, much of the wall of the bronchus may be gradually destroyed. The mucous glands are destroyed and replaced by the tuberculous foci which develop in these zones. Similarly, the granulation tissue forming the wall of the ulcer widens, separates, and gradually replaces the mucous glands.

The cartilage is affected only in the very extensive process, in which instance it is involved by the encroaching granulation tissue. As the ulcer enlarges and borders of the granulation tissue zone widen, it erodes the perichondrium irregularly and later the cartilage. Occasionally, a rapidly progressing ulcerative process containing a wide inner wall of caseation extends to and surrounds the cartilage. When this undergoes liquefaction, a sequestrum of a cartilage plate lies at the base of the ulcer.

In the cases of bronchial stenosis, the tuberculous process is a chronic one in which there has been progression and repair for some time. The wall of the bronchus is greatly thickened by granulation tissue which separates and replaces most of the mucous glands and encircles and replaces to a variable degree the cartilaginous plates. This granulation tissue extends into the surrounding tissue for variable distances and contains many small and large foci, some of which contain a central zone of caseation. The stenotic bronchus contains an irregular ulcer which in some regions is lined by a pyogenic membrane, in others by caseation which in areas is irregular and protrudes into the lumen, and in still others by granulation tissue.

Healing: Anatomic healing may occur in any stage of development of tuberculosis. It has been our experience that "tract tuberculosis" which is secondary to the original focus will in the vast majority of cases undergo healing if the source of tubercle bacilli is shut off. With closure of cavities in the lungs, healing of ulcers of the intestines, larynx, and tracheobronchial tree follows. Cavity closure follows closure of the bronchi at the bronchocavitary junction. In five instances in this series foci in the stage of anatomic healing were still present after the cavities had closed and the source of tubercle bacilli was cut off. The foci were still present from three to seven months after the closure of cavities and the disappearance of tubercle bacilli from the sputum.

In the majority of cases the tuberculous process in the trachea and bronchi is limited to small foci within the wall. When these undergo healing, they result in small areas of fibrosis and there is no distortion of the wall. Healing of ulcers occurs when the zone of vascular granulation tissue replaces the inner zone of caseation and the pyogenic membrane. With the increase of collagen fibrils, the cells and capillaries within the granulation tissue disappear and a zone of connective tissue replaces them. Regeneration of epithelium from all sides beyond the defect completely covers the ulcer. The regenerated epithelium now covers a zone of connective tissue in which an occasional capillary and epithelioid cell are present. With the final disappearance of the specific cells and capillaries the resultant connective tissue does not differ from that in noninvolved areas. At this stage it is impossible to identify this as the site of a healed ulcer. This will account for the discrepancy between bronchoscopy and autopsy findings when there is some interval between the last bronchoscopy and death. This occurs in the more chronic cases where healing of such ulcers occurs and not in the more rapidly progressing cases where the pathologist sees more extensive ulceration than the bronchoscopist.

Occasionally healing was noted in cases after much of the wall had been destroyed by deep ulceration and the presence of numerous foci. In these cases there is destruction of much of the cartilage, mucous glands, muscle, and elastic fibers. Healing results in the extensive fibrous replacement of the ulcer walls and the foci. Occasional remnants of normal structure lie within the scar tissue. Re-epithelialization of the healed ulcer is usually complete and the mucous membrane may have a smooth homogeneous surface, if the destruction was evenly distributed over one area, or a more corrugated appearance if there were irregular ulcers with intervening intact zones. In either event the circumference of the wall is greatly decreased in this region and the lumen may be narrowed to one-third of its original size (figure 3a).

DISCUSSION

There are three possible routes of infection of the trachea and major bronchi. These are: (*1*) hematogenous, (*2*) extension from the neighboring structures; and (*3*) intracanilicular infection.

Hematogenous infection: The presence of miliary tubercles in the wall without ulceration in 187 cases raises the question of whether these may not have occurred by way of the blood stream. For this assumption to be valid, the foci in the

tracheobronchial tree would have to be part of a general hematogenous dissemination and similar foci would have to be present in other organs. A terminal miliary dissemination in the form of miliary tubercles in the viscera was observed in 72 of the 187 cases. The absence of hematogenous foci in other organs in the remaining 115 cases throws doubt on this as a usual route of infection. Another strong argument against the hematogenous route is the rarity with which miliary tubercles are found in the tracheobronchial tree in cases of acute generalized miliary tuberculosis. In this series there were only 4 cases in which the tubercles were part of an acute hematogenous dissemination. We agree with Cohn and Wessler (2), who observed one such case clinically, that the tubercles so formed play little or no role clinically.

Extension from the neighboring structures: In 12 cases a neighboring tracheobronchial lymph node extended through the wall and emptied its contents into the lumen of the tracheobronchial tree. The tuberculous process in these instances was limited to the region of the perforation and the opening was sealed by the adherence of the lymph node to the adventitia of the bronchus. The mass of caseation from the perforated lymph node may protrude into the lumen of the air passage and cause a decrease in its diameter.

The perforation into the air passages occurred in persons who had a progressive caseous tuberculosis of the lymph nodes of the mediastinum. In 4 instances the involvement of the lymph nodes was part of a primary complex and occurred in children. The other 8 cases occurred in adults and were part of a lymphohematogenous tuberculosis. There was an extensive caseous tuberculosis of the lymphatic system in the latter group.

Another possible mode of extension from the neighboring structures is a lymphatic drainage into the wall of the bronchus from the neighboring structures. This view has been advocated by Reichle and Frost (3) who felt that this is a more frequent mode of infection than implantation. They believe that the infection is carried from the lungs by way of lymphatics which are located in the adventitia. The lymphatic vessels lie near the mucous glands in the extracartilaginous region. Ornstein and Epstein (4) believed this to be the mode of infection in 8 clinical cases described by them. Subsequent observers have given little support to this mode of infection.

It is difficult to accept the views of Reichle and Frost (3) since tuberculosis of the air passages is rarely limited to the adventitia and then only in the form of an occasional tubercle limited to this zone. In the remaining cases the earliest changes are first observed in the submucosa just beneath the mucous membrane. With the advancement of the tuberculous process in the wall, the changes extend outward toward the adventitia. It is the writer's impression that tuberculosis in the tracheobronchial tree, like that in the larynx and gastrointestinal tract, begins in the mucosa and submucosa and progresses outward.

Intracanilicular infection: With the exception of the occasional case of hematogenous dissemination and those with isolated foci in the adventitia, where the possibility of a lymphatic extension from a neighboring process exists, the infection of the air passages is the result of infected material passing over the mucous membrane.

The pouring out of numerous virulent tubercle bacilli must be considered an important factor since tracheobronchial tuberculosis occurs most frequently in the more rapidly progressing cases of chronic pulmonary tuberculosis. The more extensive ulceration is seen in the more acute cases of phthisis. This tendency for severe "tract tuberculosis" is not limited to the tracheobronchial tree, since these advanced cases are very often associated with extensive disease of the larynx and intestinal tract. Salkin, Cadden, and Edson (5) similarly found that the cases with tracheobronchitis showed a higher incidence of tuberculous lesions in the larynx and intestines and that it is a manifestation of a more malignant type of tuberculosis and represents a severer type.

The present observations, as well as most reports in the literature, show that tracheobronchial tuberculosis most often begins in the region of the coryna. The tubercle bacilli are carried through the lumen of the tracheobronchial tree and implanted in the wall. The corynal region corresponds to the ileocecal region of the intestinal tract as a site of predilection. Although sections of the branch bronchi in these cases will often show the presence of small foci in different parts of the walls, it is not the result of a continuous extension from the pulmonary cavities. To assume that the infection occurs by contiguity from the pulmonary infection, one would expect to see a continuous ulcerative process from the cavity along the bronchial wall. Continuous ulceration beginning at the bronchocavitary junction and extending to the major bronchus is a very infrequent occurrence in our experience. Meissner (6) examined the branch bronchi in surgically removed lungs for chronic pulmonary tuberculosis and found an irregular distribution of the tuberculous process in the various bronchi but no continuous ulceration. The present study shows that tuberculous ulcerations of the branch bronchi (except at the bronchocavitary junction where it is present in almost every case) is a very infrequent finding.

Reichle and Frost (3) believe that the strongest argument against the intracanilicular theory is the absence of bronchial tuberculosis a few centimeters from a large cavity even though large quantities of infected sputum must have passed over this mucosa daily for weeks or months. Their argument also against comparing this mode of pathogenesis with intestinal tuberculosis is that the latter has an absorbing surface whereas the bronchus has not. It would, however, be difficult to explain a lymphatic extension to the larynx which has a similar incidence of tuberculous involvement and shows a similar mode of development and extension as that in the tracheobronchial tree.

Incidence: A review of the literature shows a marked variation in the reported incidence of tracheobronchial tuberculosis at autopsy. This varies from 3.1 per cent (7) to 72 per cent (8). In a previous report from our institution, Wilber (9) reported an incidence of 35.4 per cent. Most of the pathologic studies in the past two decades report an incidence which varies from 30 to 50 per cent.

It is believed that the reason for the great variation in the incidence lies in two important factors: (*1*) the type of case, and (*2*) the extent to which the tracheobronchial tree is studied. In the present series of 1,000 autopsies, all cases of tuberculosis were included (whether or not they had active chronic pulmonary tuberculosis). Thus, there were 92 cases without pulmonary tuberculosis and 30

other cases in which the chronic pulmonary tuberculosis had undergone anatomic healing, the patients having died of other causes (amyloidosis, cardiac failure, et cetera). As emphasized previously, the presence and the extent of tuberculosis in the tracheobronchial tree very frequently go hand in hand with rapidly progressing chronic pulmonary tuberculosis.

As would be anticipated, the extent of study of the tracheobronchial tree will greatly influence the incidence of lesions. The fact that 187 cases were first discovered on microscopic examination would clearly indicate that, if reliance were placed on gross examination alone, the incidence would only be 22.2 per cent. In the microscopic study, tuberculous foci limited to the trachea or either major bronchus were found in 138 cases, of which 34 showed the presence of only one or two foci. It is believed that, if more sections had been studied from different parts of the trachea and bronchi which on gross examination had appeared normal, more foci would have been found microscopically. This is in disagreement with the views of Bugher, Littig, and Culp (10) who state that a section chosen at random will accurately describe the entire trachea with the presence or absence of tubercles. While this may hold true in a few cases, in the majority of cases in the present series it could not be verified.

Sex: Much emphasis has been laid upon the preponderance of women over men with tracheobronchial tuberculosis. The incidence has been reported as high as 72 per cent (11), 75 per cent (12), and 85 per cent (13). It is interesting to note that this observation has been made chiefly in clinical studies, although a notable exception to this is the autopsy series of Sweany and Behm (8). Our own findings show a slightly greater incidence of tracheobronchial tuberculosis in women than in the general autopsy series, but certainly not that reported in the clinical studies. This is interesting in that Myerson (14), in his clinical studies at the same institution in which this autopsy material was studied, states that women are affected three times more frequently than men. It is believed that this discrepancy may be accounted for in two ways: (*1*) Proportionately more women attend the bronchoscopic clinic than men; (*2*) many more men than women first enter the hospital in a far advanced stage of chronic pulmonary tuberculosis and are too ill to be seen by the bronchoscopist. The autopsy results as reported by Bugher, Littig, and Culp (10), Silverman (15), and Habershon (16) also show a marked preponderance of men over women.

Associated laryngeal tuberculosis: Laryngeal tuberculosis was present in 251 cases (59.6 per cent) in this series. In a previous study on laryngeal tuberculosis, the writer found an associated tracheobronchial tuberculosis in 57.5 per cent. In other autopsy reports (8 and 15), where similar comparisons were made, there is a similar frequent association.

While we agree with those authors (Bugher, Littig, and Culp (10) and Huang (17)), who claim that there is both pathologic and clinical evidence against the alleged development of a tubercuous tracheobronchitis secondary to laryngeal tuberculosis as suggested by Lederer (18), there are occasional cases (3 in this series) in which laryngeal tuberculosis may extend to the superior portion of the trachea. A similar observation was made by Samson (19) on bronchoscopic study and by Silverman (15) in autopsy cases.

In all other cases where both structures are involved, the tuberculous processes develop independently. Tracheobronchial tuberculosis develops in the corynal region most often, and laryngeal tuberculosis in the region of the vocal cords. As both processes advance, the former extends superiorly and the latter extends inferiorly, and in severe processes there may be an extensive ulcerative process which may extend from the tip of the epiglottis down into the major bronchi.

Associated intestinal tuberculosis: It is rather interesting that in 81.9 per cent of the cases in this series there was an associated gastrointestinal tuberculosis. This is easily explained by the fact that in the entire autopsy series the incidence of intestinal tuberculosis is 70 per cent and in chronic pulmonary tuberculosis it is even greater. The incidence of laryngeal tuberculosis on the other hand is 37.5 per cent (20). It is, therefore, no surprise to find a much greater association with intestinal than laryngeal tuberculosis.

The writer is in agreement with Samson, Barnwell, Littig, and Bugher (21) who state that this tract involvement is associated with a common factor, chronic pulmonary tuberculosis.

Location: The majority of the bronchoscopic and anatomic reports are in agreement with the present findings that most of the tuberculous ulcers are present in the posterior aspect of the tracheobronchial tree just above the coryna. Minkovsky (22), in a study of a large series of tracheal tuberculosis, found the most severe involvement in the majority of his cases to be in the lower part of the trachea. A notable exception is the study of Warren, Hammond, and Tuttle (23) who stated that the ulcers were not found especially along the posterior wall but rather about the orifices of the various bronchi.

It would appear from the present study that the frequency of tracheal ulceration and its relationship to bronchial ulcers is at variance with most reports, particularly the bronchoscopic observations. These authors (Acuna (24), Hawkins (25), Samson (19), and Wilson (11)) believe that ulceretion in the trachea is less frequent than in the major bronchi. Some authors state that in most instances the tracheal lesion is an extension of the bronchial disease (Hawkins and Wilson) and that in almost every instance it is found on the same side and continuous with the bronchial ulceration (Wilson).

This discrepancy is more apparent than real. Since our cases in most instances represent a progressive process, it is no surprise to find extensive ulceration of the tracheobronchial tree. The site of predilection for the ulceration is the corynal region. Thus, in progression of a tuberculous process of either major bronchus, the opportunity for extension to the trachea is great.

The presence of 47 cases of tuberculous ulceration limited to the trachea, on the other hand, shows that isolated ulcerative tracheal tuberculosis is not a rare occurrence.

Bronchial stenosis: Eloesser (26) gave this phase of bronchial tuberculosis much prominence when he stated that it was a stepchild of clinical medicine, that it was recognized too rarely, and that clinicians were not aware of how frequently it occurred. Subsequent clinical studies have emphasized the frequency of this complication in tracheobronchial tuberculosis.

Narrowing of the lumen of the tracheobronchial tree by a tuberculous process

may either be by the compression and extension of a tuberculous infection from without (extrinsic) or the development of a tuberculous process within the wall with subsequent narrowing of the lumen (intrinsic).

Extrinsic process: In this series there were 12 cases in which the lumen of the bronchus was compressed by the neighboring lymph nodes. Later the caseous node ruptured into the lumen of the bronchus.

Intrinsic process: Stenosis due to an intrinsic tuberculous process was encountered in 3 cases in this series. Prior to this study we encountered 3 similar cases. In all 6 cases there was a chronic ulcerative process with extensive destruction of the wall.

One of the 6 patients died of asphyxiation as a result of the aspiration of caseous particles to the opposite lung following bronchoscopy. Previous bronchoscopic treatments had given this patient relief when the narrowed lumen became obliterated by caseous particles and mucus. These findings appear to fit in with the views expressed by Andrews (27) that the stenosis is probably constant in this type of case at least (figure 3a), and the intermittency of symptoms is due to recurrent blocking of the narrowed lumen with caseous debris or thick mucus. Cases of asphyxiation due to a stenosis of the type just described have been reported by Schonwald (28), McConkey (29), and Crimm and Strayer (30).

It is difficult to explain the great discrepancy between the relatively great frequency of bronchial stenosis reported in clinical studies and the infrequency of such cases in the present autopsy series. Tuttle, O'Brien, Day, and Phillips (31) reported 92 such cases, of which 69 had an ulcerostenosis and 23 had a fibrous stenosis, and they state that the morbidity is great and fatality is high in ulcerostenosis. One possible explanation for the discrepancy may be the presence of an extensive edema in the wall of a bronchus containing tuberculous ulcers which greatly narrows the lumen. The edema disappears then with the patient's death. This view is given support by the clinical and pathologic studies of Salkin, Cadden, and Edson (5) who state that one form of stenosis is an inflammatory swelling which is relative and is capable of being converted later to either a true stenosis or to an almost normal appearance.

In some of the cases of rupture of a caseous lymph node into the bronchus, the node first compressed and then eroded the bronchus. The eroded bronchus in these instances was lined by an irregular border of caseation extending in from the caseous lymph node (figure 4). It is possible that some of these cases might be interpreted bronchoscopically as intrinsic bronchial stenosis.

Associated lung suppuration: Eloesser (26) states that more often than not cases of bronchial stenosis are complicated by suppurations and infections distal to the stenosis. Cohen and Higgins (32), in 19 patients with intrinsic bronchial obstruction complicating pulmonary tuberculosis, demonstrated bronchiectasis in 13, either by lipiodol installation or necropsy examination (4 cases). It should be emphasized that histological studies of the 4 necropsy cases showed tubercles in the walls of the bronchiectatic sacs and that there is no report of the isolation of pyogenic organisms. Chamberlain and Gordon (33), in a clinical study, emphasize that endobronchial tuberculosis is essentially a problem of mechanical ob-

struction with obstructive emphysema, bronchiectasis, and atelectasis as frequent complications. Other authors have also found that the sequelae of retained pyogenic organisms beyond the obstruction are fibrosis, bronchiectasis, and lung abscesses (34 and 35). It is significant that almost all of these reports are clinical studies.

The lung on the affected side in our cases was greatly diminished in size when compared with the opposite side. None showed any evidence of secondary infection and with it the sequelae which follow an obstruction of the lumen of the

FIG. 4. (Rupture of lymph node into tracheobronchial tree). (Left) Coronal section of the lungs in a 16-year-old boy who had a caseous tuberculosis of the tracheobronchial lymph nodes as part of a lymphohematogenous tuberculosis. His lung fields were clear and the sputum negative for tubercle bacilli before the rupture of the nodes into the tracheobronchial tree at the coryna. The lumen of the left major bronchus is compressed by the enlarged caseous tracheobronchial lymph nodes.

FIG. 5. (Ulceration). (Right) Coronal section of the lungs of a 16-year-old boy with chronic pulmonary tuberculosis of six months' duration. Pulmonary cavitation is limited to the right lung. Ulceration is present in the trachea and major bronchi and is most extensive in the right major bronchus.

bronchus so frequently observed in carcinoma of the major bronchus. It is interesting that the autopsy cases described by McConkey (29) and Crimm and Strayer (30) also showed changes similar to ours. Schonwald (28) in his case points out that the retained secretions contained tubercle bacilli but no other organisms.

In our experience, lung abscesses and/or suppurative inflammation of the tracheobronchial tree in the presence of chronic pulmonary tuberculosis is a rare occurrence, even under conditions where one would naturally expect them to occur. In almost every tuberculous cavity there is a great narrowing of the bronchus at the bronchocavitary junction; still it is rare to find pyogenic organisms in the vomica beyond the obstruction (36). Mixed infection tuberculous cavities are rare indeed and, even in cases of mixed infection empyema of the

pleural cavity in which bronchopleural fistulae are demonstrated, suppurative processes do not develop within the lung.

Pyogenic abscesses were present in the lungs in 2 cases in this series. These were instances of extensive tracheobronchial tuberculosis in which portions of the cartilaginous rings are partially eroded and lay exposed. There was no stenotic lesion present in the tracheobronchial tree in these cases.

Isolated tracheobronchial tuberculosis: In rare instances, at least in material observed at autopsy in a tuberculosis institution, the underlying tuberculous cavity may close and the tuberculous process within the tracheobronchial tree may progress. The writer has observed one such case which was not included in the present series. In this individual the cavity on the affected side had healed and the foci in this lung showed far advanced healing. The source of the tubercle bacilli in the sputum was the granulomatous caseous ulcer in the narrowed bronchus. Although we have observed this phenomenon in only one case, clinical observations appear to indicate that ulcerative tracheobronchial tuberculosis is not too infrequent a source of tubercle bacilli in the sputum. Alexander, Sommer, and Ehler (37) state that, with thoracoplasty in the presence of tuberculous tracheobronchitis, complete control of parenchymal lesions is not necessarily followed by anything like a corresponding improvement in the tracheobronchial lesions. Barnwell, Littig, and Culp (38) state that one of the most striking features of their 6 cases of ulcerative tracheobronchitis was the small extent of the pulmonary focus of tuberculosis when the patient first came under observation. They came to the conclusion, supported by bronchoscopic and pathologic studies, that tracheal and bronchial ulcers are a source of tubercle bacilli in the sputum. A similar view was expressed by Cohen and Wessler (2). Our case would lend some support to the claims that bronchial stenosis with caseous particles in the lumen may be responsible for tubercle bacilli in the sputum.

It is possible that ulcerative bronchitis may be a source of tubercle bacilli when the process is that of an ulcerogranuloma with large caseous particles in the lumen or that of a perforated liquefied caseous lymph node pouring tubercle bacilli into the lumen. In the usual ulcerative process after cavity closure in the lungs, the caseous inner lining, which is generally scanty, is soon replaced by granulation tissue.

SUMMARY

In a study of 1,000 consecutive autopsies on tuberculous patients, 421 were found to have tracheobronchial tuberculosis, an incidence of 42.1 per cent.

Tuberculosis of the trachea and major bronchi was in the vast majority of cases the result of an intracanilicular infection from active and progressive chronic pulmonary tuberculosis. It was part of a tendency toward "tract tuberculosis" and occurred concomitantly with laryngeal and intestinal tuberculosis in 85 per cent of cases. A few cases (12) resulted from the rupture of a caseous lymph node into the tracheobronchial tree. Only 4 cases were associated with an acute hematogenous dissemination. That isolated foci in the adventitia were found in only an occasional case and that submucosal foci were far more frequent than adventitial foci suggest that extension to the trachea and bronchi through the lymphatics is a very rare route of infection.

Intrinsic bronchial stenosis was not found as frequently in this autopsy series as in clinical studies. In 6 cases of bronchial stenosis the lung on the affected side in each instance was contracted and in none was there any evidence of suppuration or bronchiectasis beyond the obstruction.

Pyogenic suppuration of the lung in chronic pulmonary tuberculosis is extremely rare and in the 2 cases in this series was associated with sloughing tracheobronchial cartilage and not with bronchial stenosis.

SUMARIO

Tuberculosis de la Tráquea y los Bronquios Mayores

En un estudio de 1,000 autopsias consecutivas en tuberculosos, 421 revelaron tuberculosis traqueobronquial, o sea una incidencia de 42.1 por ciento.

La tuberculosis de la tráquea y bronquios mayores fué, en la inmensa mayoría de los casos, resultado de una difusión intracanalicular de una tuberculosis pulmonar crónica, activa y evolutiva. Formó parte de una tendencia a "tuberculosis de las vías", coincidiendo con tuberculosis laríngea e intestinal en 85 por ciento de los casos. Algunos (12) casos provinieron de la rotura de un ganglio caseado en el árbol traqueobronquial. Sólo 4 casos se asociaron con diseminación hematógena aguda. El hecho de que sólo se descubrieran focos aislados en la adventicia en alguno que otro caso, y de que los focos submucosos fueran más frecuentes que los adventiciales, indica que la propagación a la tráquea y bronquios a través de los linfáticos constituye una vía muy rara de infección.

La estenosis bronquial intrínseca no fué observada tan a menudo en esta serie autópsica como en los estudios clínicos. En 6 casos de estenosis bronquial, el pulmón del lado afectado estuvo siempre contraído, sin haber nunca signos de supuración o bronquiectasia más allá de la obstrucción.

La supuración pulmonar es sumamente rara en la tuberculosis pulmonar crónica, y en los 2 casos de esta serie se asoció con esfacelo del cartílago traqueobronquial y no con estenosis bronquial.

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PRESERVATION OF MYCOBACTERIA BY DESICCATION IN VACUO[1]

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INTRODUCTION

Desiccation has long been known as a good bacteriostatic method for many saprophytic organisms. Desiccation *in vacuo* has recently been shown to be an effective, simple, and inexpensive means of preserving many species of fragile parasitic bacteria in a viable state over periods from a few months to 21 years (1). This report deals with the preservation of organisms of the genus *Mycobacterium* for over 17 years by desiccation *in vacuo*, using a method very similar to that referred to above.

In 1933 Harris and Lange (2) pointed out various disadvantages of maintaining actively vegetative bacterial cultures by monthly or bimonthly subculture; strains sometimes die out, contaminations occur, and the method is expensive, time-consuming, and troublesome. An additional disadvantage is the fact that variations in biological characters, including virulence, often occur. This has introduced considerable confusion into experimental studies of tuberculosis involving such strains as H37 and B1. The advantages of a simple method of preservation which maintains bacterial cells apparently unaltered, in a state of virtual suspended animation, without subculture, manipulation, or change of environment, for many years are obvious.

During studies on the preservation of acid-fast organisms in 1931, Harris and Lange prepared a half-pint milk bottle as a preserving vessel for vacuum desiccation of bacteria according to a method described by Brown (3) and stored within it a number of vials containing various strains of *Mycobacterium*. The jar was evacuated, closed with a desiccating agent in it, and reopened after eleven months.

The organisms were found viable, as reported, in 1932 (2).

The jar was again closed and stored in an obscure corner of a large refrigerator where it remained forgotten for about seventeen years. In the meantime, Dr. Lange died and Dr. Harris left Baltimore and one of us (MF) came into possession of the bottle which had remained in the refrigerator. In 1948 the bottle was transferred to Atlanta as part of a collection of desiccated cultures prepared and maintained for over twenty-one years. There it was opened and attempts were made to activate the bacteria which had remained forgotten for so long, dried *in vacuo*.

FIRST ATTEMPT TO REACTIVATE THE CULTURES

The bottle was opened on August 5, 1948. The small manometer which had been placed inside the bottle, following the procedure of Brown, registered a

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vacuum of 43 mm., indicating virtually a perfect closure for seventeen years before the seal was broken. The following strains were selected for the first attempt at reactivation: Saranac H37 (human), B1 (bovine), B A I Pheasant (avian), and Butter R (saprophyte). The remaining strains were resealed *in vacuo* in another container and stored at refrigerator temperature. A heavy suspension of the desiccated material was prepared by adding about 0.2 ml. of Tween-albumin medium (4) to the small vials and breaking up the hard kernels with a sterile wooden applicator stick. Smears prepared from the desiccated material revealed heavily beaded acid-fast rods.

The suspension was removed from the vials and added to approximately 5 ml. of Dubos liquid (Tween-albumin) medium which served as the inoculum. Two tubes of Lowenstein-Jensen (5) medium, two tubes of Trudeau Committee (6) medium, and two tubes of Dubos Tween-albumin medium were each seeded with 0.3 to 0.4 ml. of inoculum. The cultures were incubated at 37°C. Animal inoculations were also made with the suspended desiccated material as described later on.

On September 9, 1948, 4 human, 2 bovine, 2 avian, and 2 saprophytic strains were suspended in Tween-albumin medium as previously described and the suspension was used to inoculate two Lowenstein slants and two tubes of Tween-albumin medium for each strain, following the same procedure as described above.

On October 27, 1948, 3 more bovine strains, 4 avian strains, and 6 saprophytes were suspended in Dubos medium, then inoculated onto Lowenstein and Dubos media as before. No animals were inoculated with suspensions of the desiccated material in the last two series of cultures. Thus, a total of 5 human, 6 bovine, 7 avian, and 9 saprophytic strains were tested for viability by inoculation on to solid and liquid media.

RESULTS OBTAINED WITH DESICCATED MATERIAL

All of the human strains grew well on solid media and 4 grew in Tween-albumin medium. Three of the bovine strains grew well on Lowenstein medium while the other 3 grew with contaminants only in Dubos medium and were overgrown by contaminants on solid media. Pure cultures were obtained from the contaminated cultures and these were used for animal studies. These data are summarized in table 1.

VIRULENCE TESTS

Desiccated material: Dense suspensions in Tween-albumin medium were prepared on August 5 from the desiccated material of one vial each of the four major types: Saranac H37 (human), B1 (bovine), B A I Pheasant (avian), and Butter R (saprophyte). Each strain was inoculated subcutaneously into the inguinal region of guinea pigs, two animals being used for each strain. Bovine and avian strains were also inoculated intravenously into rabbits.

The desiccated bovine strain produced a few small lesions on the spleen of one of the guinea pigs, while the other guinea pig and the rabbit showed no

lesions. The human, avian, and saprophytic strains failed to produce any lesions in the animals inoculated with the desiccated culture material.

TABLE 1

Results of Attempts to Reactivate Acid-fast Bacilli Preserved by Desiccation in vacuo for 17 Years

STRAIN*	GROWTH UPON MEDIUM OF	
	Lowenstein	Dubos (Tween-albumin)
Human		
Saranac H37	+ (2) †	—
Lov. 7	+ (2)	+ (1)
Lov. 9	+ (2)	+ (1)
Lov. 62	+ (2)	+ (1)
Lov. 71	+ (3)	+ (1)
Bovine		
B 1	− ‡	+ ‡ (1)
Princeton 32	− ‡	+ ‡ (1)
Park 643	− ‡	+ ‡ (1)
Zinsser B 1	+ (3)	+ ‡ (2)
Opie B 1	+ (2)	—
Hyg. Lab. 410	+ (2)	—
Avian		
B A I Parrot	+ (2)	—
B A I Pheasant	+ (2)	+ (1)
B A I Swine	+ (3)	+ (1)
Van Es. H3701	− ‡	+ ‡ (1)
Van Es. 3732	+ (2)	+ (1)
Van Es. 4957	+ (3)	+ (1)
Van Es. Stock	+ (2)	+ (2)
Saprophytes		
Butter R	+ (1)	+ (1)
Timothy 6292	+ (1)	+ (1)
Saranac Timothy	+ (1)	+ (1)
Saranac "lepra B"	+ (1)	+ (1)
B. leprae A. M. "Apa"	+ (1)	+ (1)
B. moelleri	+ (1)	+ (1)
B. smegmatis	+ (1)	+ (1)
B. E. S.	+ (1)	+ (1)
Red Timothy	+ (1)	+ (1)

* Nothing is known of the history or origin of the strains other than what may be inferred from the names given, which are those found on the original vials.

† Numbers in parentheses indicate weeks after which growth was first recorded.

‡ Contaminated.

Pure cultures: One-week-old cultures of the saprophytes grown on Lowenstein-Jensen medium were suspended in sterile saline to give a final concentration of 5 mg. per ml. Guinea pigs were inoculated subcutaneously in the inguinal region with 1.0 ml. of each suspension.

The pathogenic strains were grown for two weeks on Lowenstein-Jensen

TABLE 2

Autopsy Findings in Animals Inoculated with Subcultures of Desiccated Acid-fast Bacteria

STRAIN	INOCULUM (mg.)	ANIMAL	DEATH†	MICROSCOPY‡	LESIONS IN‖					VIRULENCE§
					Lungs	Liver	Spleen	Nodes	Kidney	
Human										
Saranac H37	1	G. P.	K-42	+	−	−	−	+**	−	?
Lov 7	10^{-1}	G. P.	K-42	+	++	++	+++	+++	−	+
Lov 9	10^{-1}	G. P.	K-42	+	++	++	+++	+++	−	+
Lov 62	10^{-1}	G. P.	D-35	+	−	+	+++	+++	−	+
Lov 71	10^{-1}	G. P.	K-42	+	++	++	+++	+++	−	+
Bovine										
B 1*	1	G. P.	K-42	+	++	++	+++	+++	−	+
	1	Rabbit	K-57	+	+++	−	+	−	+	+
Zinsser B 1	10^{-1}	G. P.	K-42	+	−	+	+++	+++	−	+
	10^{-1}	Rabbit	K-60	+	+++	−	−	−	+	+
Opie B 1	10^{-1}	G. P.	K-42	+	−	++	++	+++	−	+
	10^{-1}	Rabbit	K-60	+	+	−	−	−	−	+
Hyg. Lab. 410	10^{-1}	G. P.	K-42	+	++	++	+++	+++	−	+
	10^{-1}	Rabbit	K-60	+	++++	−	−	−	−	+
Avian										
B A I Parrot	1	G. P.	K-42	−	−	−	−	−	−	−
		Chicken	D-60	−	−	−	−	−	−	−
B A I Swine	1	G. P.	K-42	−	−	−	−	−	−	−
		Chicken	K-60	−	+ (Atyp.)	−	enlarged	−	−	−
Van Es 3732	1	G. P.	K-42	+	−	−	+	+	−	Undetermined
		Chicken	D-19	−	−	−	−	−	−	Undetermined
Van Es 4957	1	G. P.	K-42	+	−	−	−	+	−	−
		Chicken	K-50	+	+++	++++	++	−	−	+
Van Es Stock	1	G. P.	K-42	−	−	−	−	−	−	−
		Chicken	D-35	+	−	−	−	−	−	+ (Yersin type)
B A I Pheasant	10^{-1}	G. P.	K-45	+	−	−	−	+	−	−
		Rabbit	K-84	+	−	−	−	−	−	+ (Yersin type)
Saprophyte										
Butter R	5	G. P.	K-42	−	−	−	−	−	−	−
Timothy 6292	5	G. P.	K-42	−	−	−	−	−	−	−
Saranac Timothy	5	G. P.	K-42	−	−	−	−	−	−	−
"Lepra B"	5	G. P.	K-42	−	−	−	−	−	−	−
B. Leprae A.M.	5	G. P.	K-42		−	−	−	−	−	−
B. moelleri	5	G. P.	K-42	−	−	−	−	−	−	−
B. smegmatis	5	G. P.	K-42	−	−	−	−	−	−	−
B. E. S.	5	G. P.	K-42	−	−	−	−	−	−	−
Red Timothy	5	G. P.	K-42	−	−	−	−	−	−	−

* Desiccated material direct.

† Figures in this column are days from inoculation. K = Killed; D = Died.

‡ Acid-fast rods seen (+) or not seen (−).

§ Virulent (+) or avirulent (−).

‖ Relative numbers of tubercles or extent of lesions are indicated by plus signs + to ++++.

** Superficial inguinal node only.

medium, then suspended in sterile saline to give the following suspensions: human 10^{-1} mg. per ml.; bovine, 10^{-1} mg. per ml.; and avian, 1 mg. per ml. One ml. of each suspension was inoculated subcutaneously into the inguinal region of a guinea pig. One rabbit was inoculated intravenously with 1.0 ml. of each bovine suspension and one chicken was inoculated intravenously with 1.0 ml. of each avian suspension.

All guinea pigs surviving forty-two days after inoculation were killed and autopsied while the rabbits and chickens were killed after sixty days. The lymph nodes, spleen, liver, and lungs of the guinea pigs and rabbits were examined for macroscopic lesions. Smears were prepared from the lesions, stained by the Ziehl-Neelsen technique and examined for acid-fast bacilli. The mesenteric lymph nodes, spleen, liver, and kidneys of the chickens were examined. Smears were prepared and examined for acid-fast bacilli. Virulence tests were not done on Princeton 32 (bovine), Park 643 (bovine), and Van Es H3701 (avian) because the cultures were lost through contamination. The results of the virulence tests are summarized in table 2.

As seen in the table, all of the strains on which tests were completed were found to be fully virulent except that Saranac H37 (human) appeared to be avirulent for guinea pigs, while Opie B 1 (bovine) was virulent for the guinea pig but exhibited low virulence in the rabbit. The strains B A I Parrot and B A I Swine (avian) were avirulent for chickens.

No exact data are available as to the original virulence of these strains. There is reason to believe that some laboratory stock cultures of the H37 and B1 strains used by investigators in 1931 were of low virulence (7). Fairly extensive lesions were produced by these strains in guinea pigs inoculated in 1932 (2). Rabbits were not inoculated at that time. It is impossible to state whether or not changes in virulence of the other organisms in this series occurred, because no exact information is available as to the level of their virulence when first desiccated.

SUMMARY

Twenty-seven strains of acid-fast bacilli were involved in this study. Of these, 18 were *M. tuberculosis* (5 human, 6 bovine, and 7 avian), and 9 were various saprophytes (such as *M. smegmatis*, *M. leprae*, "timothy" (*M. phlei*)). These bacteria were desiccated in a vacuum bottle in 1931, stored in a refrigerator, and remained undisturbed for seventeen years until 1948 when the bottle was opened and attempts were made to reactivate the cultures.

On introduction into appropriate media, all strains grew readily. Their morphology, staining properties, and virulence appeared unchanged. A few were lost because of overgrowth by contaminants, but sufficient growth of acid-fast bacilli occurred to demonstrate the viability of microorganisms. One human (Saranac H37), one bovine (Opie B 1), and two avian (B A I Parrot and B A I Swine) strains of *M. tuberculosis* were avirulent but all of the other strains of tubercle bacilli were fully virulent. No data were available as to the state of virulence of the cultures when originally desiccated, but it is thought that the human strain H37 may have been of low virulence to begin with.

CONCLUSIONS

Desiccation *in vacuo* is a simple, inexpensive, readily available method of preserving acid-fast bacilli for long periods of time. The only special equipment needed is a good vacuum pump, a one-pint Mason jar, a dehydrating agent ($CaSO_4$), and plasticine or other plastic material (1). With this method, standard laboratory strains, including freshly isolated strains and "vaccine strains", may be stored or shipped great distances without difficulties or concern over space, dehydration, or breaking up of culture media.

SUMARIO

Conservación de las Micobacterias por la Desecación al Vacío

En este estudio figuraron 27 cepas de bacilos acidorresistentes: 18 del *M. tuberculosis* (5 humanas, 6 bovinas y 7 aviarias) y 9 de varios saprofitos (tales como, *M. smegmatis, M. leprae, M. phlei*). Esas bacterias fueron desecadas en un frasco al vacío en 1931 y colocadas en un refrigerador, en el que permanecieron sin ser tocadas durante diecisiete años, hasta 1948, fecha esta en que se abrió el frasco y se trató de reactivar los cultivos.

Al ser introducidas en medios apropiados, todas las cepas proliferaron sin dificultad, sin cambio aparente en morfología, propiedades de tinción y virulencia. Algunas se perdieron por excesivo desarrollo de gérmenes contaminantes, pero hubo suficientes colonias de bacilos acidorresistentes para demostrar la viabilidad de los mismos. De las cepas de *M. tuberculosis*, una humana (Saranac H37), una bovina (Opie B1) y 2 aviarias (B A I Papagayo y B A I Cerdo), resultaron avirulentas, pero todas las demás eran plenamente virulentas. No hay datos relativos al estado de virulencia de los cultivos al ser desecados primitivamente, pero parece que la cepa humana H37 puede haber poseído poca virulencia para dicha fecha.

CONCLUSIONES

La desecación al vacío ofrece un método sencillo, económico y de fácil empleo para la conservación de bacilos ácidorresistentes durante períodos de tiempo prolongados. La única instalación especial necesaria consiste en una bomba neumática, un jarro de Mason de ½ litro, un deshidratador ($CaSO_4$) y plasticina u otra sustancia plástica. Con este método, sin dificultad y sin preocuparse con respecto a espacio, deshidratación o desintegración de los medios de cultivo, pueden conservarse o remitirse a grandes distancias cepas corrientes de laboratorio, incluso las recién aisladas y las destinadas a la producción de vacunas.

Acknowledgment

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TOXICITY OF SPUTUM D'GESTANTS TO TUBERCLE BACILLI IN WATER AND SPUTUM[1]

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INTRODUCTION

Isolation of *M. tuberculosis* from contaminated pathological material can best be accomplished if proper methods of digestion and decontamination are used. Cultivation of *M. tuberculosis* on artificial media is slow and difficult, and requires special methods to prevent the multiplication of contaminating organisms commonly found in specimens from which tubercle bacilli must be isolated. It is essential that the methods employed to reduce contamination do not retard growth of tubercle bacilli. Despite the many improvements which have been suggested in cultural techniques, it is not always possible to initiate growth in cultures from microscopically positive specimens.

Preparation of specimens for smear, culture, or animal inoculation by digestion and concentration necessitates exposure of the material to various more or less toxic substances. The purpose of such treatment is to dissolve tenacious mucus and cellular debris and to kill secondary organisms. Theoretically an ideal digestant should be toxic to all organisms except the tubercle bacilli. This study was undertaken to help evaluate the relative toxicities of the most commonly used digestive agents.

The work is divided into two parts: (*1*) preliminary laboratory tests on aqueous suspensions of tubercle bacilli; (*2*) tests on homogenized sputum under practical diagnostic conditions.

METHODS

Aqueous Suspensions

A 3-weeks-old culture of H37Rv was harvested, weighed, and ground ten minutes in a sterile mortar with enough sterile distilled water to prepare a suspension containing 1 mg. of the bacilli per ml. Dilutions were prepared from this suspension containing 10^{-3} and 10^{-4} mg. of bacilli per ml. Each dilution was divided into 1 ml. amounts and mixed with equal volumes of the digestant: 4 per cent sodium hydroxide, 3 per cent hydrochloric acid, 5 per cent sulfuric acid, 2.5 per cent ammonium carbonate, and 10 per cent trisodium phosphate (anhydrous).

Exposure of the tubercle bacilli to the various digestants was brought about by combining the digestant in question, in the concentrations routinely employed with an equal volume of the bacilli in water, incubating for the desired interval at 37°C., mixing with a predetermined quantity of neutralizing agent (all such mixtures were adjusted to 10 ml. volume) and then seeding in amounts of 0.1

[1]From the Tuberculosis Evaluation Laboratory, Communicable Disease Center, Public Health Service, Atlanta, Georgia.

ml. on each of 10 tubes of Jensen's modification of Lowenstein's medium. The total weight of bacilli thus transferred was 10^{-5} or 10^{-6} mg. per tube of medium, according to the dilution used. This same procedure was repeated in testing each different period of exposure, each digestant, and each dilution of bacilli. In general the exposures were 40 minutes, 24 hours, 48 hours, and 72 hours.

Inoculations were made from the mixtures onto Jensen's modification of Lowenstein's medium (1) after exposing the bacilli for measured periods of time to the digestants. Controls were prepared by adjusting the reaction of the digestants to pH 7.0 before combining with the proper weight of culture. In a

TABLE 1

Total Colony Counts on 10 Tubes of Medium Inoculated with Aqueous Suspensions of Tubercle Bacilli Exposed to Various Digestants

EXPOSURE TIME	5 PER CENT Na_3PO_4		2 PER CENT NaOH		1.25 PER CENT AM. CARB.		2.5 PER CENT H_2SO_4		25 PER CENT ANTIFRM.		1.5 PER CENT HCl	
	Count	Per cent Surv.	Count	Per cent Surv.	Count	Per cent Surv.	Count	Per cent Surv.	Count	Per cent Surv.	Count	Per cent Surv.
					10^{-5} mg. Bacilli Per Tube							
Control*	582	100.0	506	100.0	163	100	478	100.0	157	100.0	100	100
40 Minutes	307	52.0	235	46.0	98	60	200	41.8	11	7.2	6	6
24 Hours	286	49.2	40	8.0	0	0	0	0	0	0	0	0
48 Hours	275	47.3	27	5.4	0	0	0	0	0	0	0	0
72 Hours	262	44.9	15	3.0	0	0	0	0	0	0	0	0
					10^{-6} mg. Bacilli per Tube							
Control*	173	100.0	68	100.0	48	100	93	100	79	100	83	100
40 Minutes	96	56.0	60	88.0	40	87	27	29	0	0	0	0
24 Hours	94	53.6	6	8.8	0	0	0	0	0	0	0	0
48 Hours	91	53.0	5	7.3	0	0	0	0	0	0	0	0
72 Hours	71	42.4	0	0	0	0	0	0	0	0	0	0

* Medium inoculated immediately after mixing bacillary suspension and neutralized digestant (pH 7).

measure these served as controls because they gave an approximation of the number of bacilli present without the prolonged action of the digestants.

A carry-over of the neutralized salts of the digestants and neutralizing agent in the inoculum to the culture was recognized but, since the same salts were also inoculated onto the control tubes, this factor was not considered important.

The cultures were examined after two weeks of incubation and once weekly thereafter until five weeks of age. The total number of colonies present at five weeks on each set of 10 tubes was counted and recorded for comparisons. Repeated experiments, inoculating 10^{-5} and 10^{-6} mg. of bacilli per tube of medium as described, gave essentially the same results each time. For the sake of brevity the results of only one experiment are given (table 1).

RESULTS

Aqueous Suspensions

From the results in table 1, it is evident that all of the digestants markedly reduced the number of viable bacilli within the shortest period likely to produce adequate decontamination. This table indicates that trisodium phosphate and sodium hydroxide are less toxic than the other agents tested. It is difficult to interpret the significance of the differences obtained with ammonium carbonate, sulfuric acid, antiformin, and hydrochloric acid. It is recognized that colony counts are somewhat variable but repeated tests gave similar results. The concentrations given are those actually in contact with the tubercle bacilli. It may be noted that the action of trisodium phosphate differs from that of the other reagents. Though approximately 50 per cent of the tubercle bacillus population was killed during 40 minutes, few microorganisms were destroyed during the remainder of the 72-hour period.

Sputum Suspensions

Because of the possible protective effect of sputum (2) on tubercle bacilli, experiments in the absence of this material might portray an inaccurate picture of the relative toxicities of various digestants under practical conditions.

With this in mind 10 microscopically "positive" specimens of sputum were pooled and homogenized by shaking two hours in a paint-conditioning machine (3). This resulted in a completely uniform, slightly viscous fluid. In this experiment the following digestants were used: sodium hydroxide, trisodium phosphate, oxalic acid, sulfuric acid, ammonium carbonate, and hydrochloric acid. Each digestant was then mixed in 1 ml. amounts with equal volumes of the homogenized sputum and allowed to incubate for the desired time at 37°C. After the specified intervals the pH of the mixtures was adjusted to 7 with the necessary amount of acid or base in sufficient diluent to make a final volume of 10 ml.,[2] and inoculated onto 10 tubes of medium in 0.1 ml. amounts without further preparation.

The exposure periods during which the "positive" sputum was in contact with each of the digestants before neutralization were 20 and 40 minutes and 2, 24, 48, and 72 hours.

In order to compare the inherent toxicities of the reagents (apart from the pH produced), aliquots of the decontaminated and neutralized sputum were also incubated in a final volume of 10 ml. of the salt formed by neutralization of each digestant. These results did not differ from those obtained when sodium hy-

[2]The homogenized sputum was tested for combining power with different digestants, sodium hydroxide, sulfuric acid, hydrochloric acid, oxalic acid, trisodium phosphate, and ammonium carbonate. Three 1 ml. samples of each digestant were mixed with 1 ml. samples of the homogenized sputum and the reaction adjusted to pH 7.0 using bromthymol blue as an indicator; sodium hydroxide was used to neutralize the acids and sulfuric acid to neutralize the bases. To avoid the use of strong reagents on metaproteins, the neutralizing solutions were brought to a volume of 8 ml.

droxide was neutralized with sulfuric acid. The loss of viability was very slow by comparison with that in the active reagents.

The toxicities of the digestants tested in the presence of sputum are shown in table 2. The toxicities of such digestants as were tested both in sputum and aqueous suspensions are seen to be comparable. Unfortunately antiform and oxalic acid were not tested under both conditions.

TABLE 2

Total Colony Counts on 10 Tubes of Medium Inoculated with Homogenized Sputum Containing Tubercle Bacilli and Exposed to Various Digestants

EXPOSURE TIME	NaOH 2 PER CENT		TRISODIUM PHOSPHATE 5 PER CENT	OXALIC ACID 2.5 PER cent	H_2SO_4 2.5 PER CENT	AMMONIUM CARBONATE 1.25 PER CENT	HCl 1.5 PER CENT
	Full time exposure	Base* only 40 minutes					
20 Minutes..	Inn. contam.	Inn. contam.	Inn. contam.	Contam.	Inn. contam.	Contam.	400
40 Minutes..	Inn.	Inn.	Inn.	Inn.	Inn.	Inn.	140
2 Hours....	Inn.	Inn.	Inn.	Inn.	1,000	1,000	0
24 Hours....	580	1,000	1,000	0	0	0	0
48 Hours....	0	700	270	0	0	0	0
72 Hours....	0	400	60	0	0	0	0

Inn. = Innumerable acid-fast colonies.

Contam. = contaminated.

* At 40 minutes the remainder of this series of NaOH tubes was neutralized.

Subsequent decline in viability serves to indicate the rate of death in neutralized sputum during the completion of the experiment.

DISCUSSION

Tison (4) claims that tubercle bacilli retain viability and infectivity up to 3 months in sputum held at 7° to 22°C., whereas in most sputum infectivity is lost after 4 days at 37°C.

Corper and Stoner (5) point out that trisodium phosphate in a concentration of 10 per cent (23 per cent $Na_3PO_4 \cdot 12H_2O$) can remain in contact with small numbers of tubercle bacilli for as long as seven days at room temperature without destroying all of them.

Results of the experiments described in this paper tend to corroborate the findings of the latter two authors. Nevertheless, even in the case of the least toxic of the digestants, a marked diminution in the number of bacilli was found after short exposures. While our experiments were never continued for as long as 7 days, it is recognized as possible that some bacilli might survive that long if their original number is large enough and the temperature of the room is low enough.

In some laboratories sulfuric acid has been considered less toxic to tubercle bacilli than either hydrochloric acid or sodium hydroxide. For this reason "thin" specimens not requiring a potent digestant are generally treated with sulfuric acid in preference to sodium hydroxide. This conception probably stems from

the work of Corper and Uyei (6) who found that, of the large number of reagents investigated for isolating tubercle bacilli from contaminated tuberculous material, sulfuric acid was most serviceable. "It possessed a wider range between its being innocuous for tubercle bacilli and its being capable of destroying undesirable contaminators than any of the others tested. HCl and NaOH also proved satisfactory for this purpose, the former slightly more so than the latter, while urea, sodium carbonate, ammonium hydroxide and ammonium carbonate proved entirely unsatisfactory."

An explanation of these findings with the acids may rest in part on the likelihood of more efficient collection of the tubercle bacilli due to their occlusion in the bulkier sediments which result from acid treatment. Low toxicity of digestant and facilitation of collection need not go hand in hand.

According to the results of tests by the Tuberculosis Evaluation Laboratory, ammonium carbonate was also found less satisfactory than the other reagents. However, repeated tests failed to show any advantage of sulfuric acid or hydrochloric acid over sodium hydroxide at any concentration studied. Two per cent, 3 per cent, and 4 per cent sodium hydroxide were compared with 2.5 per cent, 5 per cent, and 6 per cent sulfuric acid and 1.5 per cent and 3 per cent hydrochloric acid. Contrary to the experience of Corper and Uyei, it was found that sodium hydroxide was relatively less toxic to the tubercle bacillus than sulfuric acid and hydrochloric acid at the concentrations mentioned and relatively more toxic than trisodium phosphate, 10 per cent.

CONCLUSION

Experiments were undertaken to compare the toxicities of various commonly used digestants. Trisodium phosphate and sodium hydroxide appeared to be less toxic to tubercle bacilli than the other agents tested.

CONCLUSIONES

Toxicidad de los Digestantes del Esputo para los Bacilos Tuberculosos en Agua y en Esputo

En las condiciones de los experimentos aquí descritos, los digestantes del esputo investigados ocuparon, en el orden de su toxicidad creciente, los siguientes puestos: fosfato trisódico, hidróxido de sodio, ácido oxálico, ácido sulfúrico y ácido clorhídrico.

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THE COMBINED USE OF TRACHEAL LAVAGE AND CULTURE AS A DIAGNOSTIC PROCEDURE IN PULMONARY TUBERCULOSIS[1, 2]

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INTRODUCTION

The clinical evaluation of the minimal pulmonary infiltration is often difficult because of lack of bacteriological confirmation. This has always been true, but with the wide use of roentgenographic surveys the problem of determining whether or not a minimal lesion is active is being encountered with increasing frequency.

The chest physician often faces the following dilemma: Should he actively treat a patient who, in his judgment, has an active lesion but from whom no tubercle bacilli can be recovered? To do so means embarking that person upon a long course of treatment with the interruption of normal living, no small expense, psychic trauma, et cetera; and yet not to treat him actively calls for prolonged observation of one who does not consider himself to be ill, and incurs the risk of losing contact with the patient. It also means that the physician must accept the hazard of possible extension of the patient's disease and infection to his near associates.

Hilleboe advises observation of these patients. If an ideal follow-up and case-holding program are available, this is good epidemiology but does not always serve the best interest of the individual. Hilleboe is rightly concerned in avoiding the treatment of inactive lesions but, unless some accurate method of evaluating activity is available, there also exists the serious possibility that the treatment of active lesions may be delayed. This may be disastrous to the individual, and the individual after all is one of the physician's responsibilities. Consequently, the one upon whom the responsibility of decision rests is relieved if he has factual data regarding the activity of the lesion under consideration.

It would seem that the answer to this dilemma would lie in the availability of a sensitive, accurate, rapid, and simple method for the recovery of tubercle bacilli from the lesion in question. A very considerable advance has been made in this direction by the combined use of tracheal lavage and sensitive culture methods. The writers have been surprised by the high percentage of recovery of tubercle bacilli from such lesions by the combined use of these procedures.

For the purpose of this discussion it is assumed that all the usual methods of direct examination have been employed without success before the more elaborate and sensitive methods are undertaken.

[1] Presented at the annual meeting of the California Trudeau Society in San Francisco, California, on April 4, 1949.

[2] Much of the data used in this paper is from a study supported in part by the Alameda County Tuberculosis and Health Association.

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ADVANTAGES OF TRACHEAL LAVAGE

Tracheal lavage as compared to gastric lavage has the following advantages:

(*1*) The material is obtained nearer the source of its origin and has not been diluted or dissipated.

(*2*) The organisms have not had their viability impaired by coming in contact with gastric acids and enzymes (important in culture or animal study).

(*3*) It is not necessary to do the tracheal lavage upon a fasting stomach. It can be done any time of the day and is easily carried out as an office procedure.

(*4*) It is well tolerated by the patient; many patients state that "it is not nearly so bad as a gastric."

Culture, when carried out by a technician trained in its use and under the exacting conditions required, has the following advantages over animal inoculation:

(*1*) It is more rapid. When using Dubos media, positive cultures are obtained not infrequently within the period of ten days, but in an average from fourteen to twenty-one days.

(*2*) It is less expensive.

(*3*) It is at least as sensitive as animal inoculation.

(*4*) In spite of belief to the contrary, there is evidence that guinea pigs have some natural resistance to infection with the tubercle bacillus (1).

These combined advantages add up to a major advance in our ability to recover tubercle bacili from the patient who sheds only a few organisms.

TECHNIQUE OF TRACHEAL LAVAGE

The technique of tracheal lavage is not difficult. Fasting is not required. If the patient has an active gag reflex, the pharynx may be sprayed with a 2 per cent pontocaine solution. For the very rare patient who may be sensitive to pontocaine, it is well to have an injectable barbiturate at hand. With the patient in a sitting position the tongue is drawn forward, the larynx is visualized with a mirror, and the laryngeal cannula tip is introduced between the vocal cords thus ensuring the introduction of the lavage liquid into the trachea itself. Then 5 cc. of sterile distilled water are quickly introduced through the cannula. The use of sterile distilled water is preferred to saline solution, since it has been reported that saline slows the growth of cultures of tubercle bacilli (2). The material coughed up is collected in a sterile container and concentrated for culture or guinea pig inoculation. Several tracheal instillations may be carried out at one sitting. The equipment required for tracheal lavage is simple and consists of the following:

(*1*) No. 4 laryngeal mirror.
(*2*) A metal laryngeal cannula.
(*3*) A 5 cc. syringe.
(*4*) A head mirror.

Because of the explosive character of the cough which sometimes occurs, it is well to wear a face mask or shield.

COMPARISON OF MEDIA

Extensive experiments have been carried on in attempts to compare various media. Such studies are never without bias of some sort, since even the most scrupulous attempts to conduct a fair trial are usually shaded in favor of the medium with which the technician is most familiar. The technical details of the media used in the present study are being published elsewhere. Suffice it to say that in the writers' experience the media used line up as follows with regard to both sensitivity and speed of growth:

(*1*) Dubos (oleic acid, solid medium with penicillin (3)).
(*2*) Herrold's medium (as described in the proceedings of the Staff Meetings of the Mayo Clinic (4, 5)).
(*3*) Official medium of the American Trudeau Society as modified at the latest session of the Research Committee (6).
(*4*) Petragnani's medium.
(*5*) Petrick's medium. (This medium was used in the laboratory for years and it is fairly sensitive, but requires considerable time for growth).

The above mentioned modified Dubos medium lends itself very well to the determination of sensitivity tests and overcomes the objections made by Williston and Youmans (7) and others, since it does not contain Tween or serum.

Dubos media in a solid form has been used to facilitate the study of the morphology of the colonies, which varies considerably. The morphology of the colonies gives an excellent index to virulence.

TRACHEAL LAVAGE AS COMPARED TO GASTRIC LAVAGE

Tracheal lavage was performed on 199 patients with negative bacteriologic findings by direct methods of examination at Arroyo del Valle Sanatorium, Highland Hospital, Fairmont Hospital (all of Alameda County), and elsewhere. Tubercle bacilli were cultured (on Dubos medium) from the lavage specimens of 111 of these 199 patients. Gastric lavage had been performed in 86 of these 111 patients. In only 24 instances was the specimen of gastric washings positive for tubercle bacilli when cultured by various techniques.

In no instance were tubercle bacilli cultured from gastric lavage material obtained from a patient whose tracheal lavage specimens were negative for tubercle bacilli.

GUINEA PIG INOCULATION AS COMPARED TO CULTURE (DUBOS)

Forty divided specimens were inoculated into guinea pigs and upon culture media. Twenty-seven of these were positive for *M. tuberculosis* upon Dubos culture, and 23 of the 27 were positive as reflected by the presence of gross lesions in the guinea pigs at autopsy. The remaining 4 animals which had been inoculated had positive tuberculin tests to 5 mg. of Old Tuberculin.

Since the start of this study two years ago at Arroyo del Valle and at Livermore Veterans Administration Hospital, there has been no instance of a "positive" guinea pig and a "negative" Dubos culture when examinations were done upon divided specimens.

GUINEA PIG INOCULATION AS COMPARED TO DUBOS MEDIUM AND AMERICAN TRUDEAU SOCIETY MEDIUM INOCULATION

Specimens obtained from 580 consecutive cases of tuberculosis were studied at Arroyo del Valle and Livermore Veterans Administration Hospital. Tubercle bacilli were cultured from the specimens from 269 patients. The specimens from 45 patients, however, yielded tubercle bacilli when cultured on Dubos medium but not upon guinea pig inoculation. The animals were tested with 5 mg. of Old Tuberculin and were examined for the presence of gross lesions at autopsy. Thirty-one of these 45 specimens also yielded tubercle bacilli when cultured on the American Trudeau Society medium.

All of the above 45 cases, which were positive to culture but negative to guinea pig inoculation, were checked by subinoculation into guinea pigs and all of the animals so inoculated developed positive tuberculin tests and had gross lesions at autopsy.

This should not be interpreted as a recommendation to abandon guinea pigs for diagnostic purposes. In hospitals which do not specialize in tuberculosis work, they furnish the best method of diagnosis, and even in laboratories devoting much time to tuberculosis they are often necessary for proof of pathogenicity.

CONCLUSION

It is believed that the combination of tracheal lavage plus culture brings us to a new era in our ability to evaluate properly the clinical status of minimal tuberculous lesions. The technique is sensitive, accurate, rapid, and the procedure of gathering material for examination is simple to perform.

The sensitiveness of these combined techniques is such that we are not yet prepared to use the procedure in evaluation of therapy. At present it is doubtful whether it should be used for this purpose. It is, however, a procedure that is of tremendous help diagnostically in evaluating lesions for which we previously had to depend to a large extent upon our clinical judgment alone.

CONCLUSIONES

Empleo Combinado del Lavado Traqueal y de los Cultivos como Procedimiento de Diagnóstico en la Tuberculosis Pulmonar

Opina el A. que la combinación del lavado traqueal y de los cultivos nos lleva a una nueva era en nuestra capacidad para justipreciar el estado clínico de las lesiones tuberculosas mínimas. La técnica es delicada, exacta, rápida y el procedimiento para recoger el material para examen es sencillo en su ejecución.

Tan delicadas resultan esas técnicas combinadas que el A. no se siente todavía en aptitud de usar el procedimiento para la valuación de la terapéutica, y duda que deba usarse para ese fin por ahora. No obstante, la técnica posee inmenso valor diagnóstico para justipreciar lesiones en las que antes había que atenerse en gran parte exclusivamente al juicio clínico.

Acknowledgment

A considerable portion of the data comparing guinea pigs with egg yolk media and (in his case) liquid Dubos media were obtained from Mr. Jack L. Wallace of the Veterans Administration Hospital in Livermore.

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AUSCULTATION

A New Conception of the Respiratory Murmur and Its Place in Diagnosis

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When one suggests the displacement of an established opinion, he should offer a logical substitute. In previous publications (1, 2, 3, 4) the writer made a new appraisal of auscultation based on clinical experience and facts in physics and physiology which have been discovered since Laennec's time. He now wishes to add further evidence to show that the respiratory murmur is composed of sound vibrations which originate in all component parts of the respiratory mechanism, and to point out how this fact may be used advantageously in the physical examination of the lungs.

For more than a century auscultation has been accepted as the chief measure on which dependence can be placed in the physical diagnosis of diseases of the lungs and pleura; and yet, as taught, it is not satisfactory. This is a prime reason why physical diagnosis in chest diseases has been disappointing and why its place has been yielded so willingly to the roentgenogram. On the other hand, could physical examination be satisfactory, the personal element in it should make it an invaluable procedure.

No matter if we are obliged to change our opinion as to the cause of the normal and abnormal respiratory murmurs, this can in no way take away the value of auscultation; or remove from Auenbrugger (5) and Laennec (6) the honor of having founded physical examination of the chest.

Laennec said: "The sound of respiration presents different characters, according as it takes place in the pulmonary tissue, the larynx, the trachea, or the large bronchial trunks." He described vesicular respiration thus: "a gentle but extremely distinct murmur, which indicates the penetration of air into the pulmonary tissue, and its expulsion." It may be heard best "where the lungs are nearest the surface of the body, namely, the anterior-superior, lateral and posterior-inferior parts."

He designated: "as bronchial respiration, the sound produced by inspiration and expiration, in the larynx, trachea, and large bronchial trunks situated at the roots of the lung .... After the roots of the lungs, the summits are the parts of these organs where the bronchial respiration is manifested in the most characteristic manner." He practically ignored expiration, but his associates described the length of inspiration to expiration as 10:2.

Beau (7) in 1834 suggested that the respiratory murmur is caused by air passing through the glottis, the sound being transmitted and modified by the bronchi and air cells, as suggested by Laennec.

Textbooks for the past century have almost universally accepted the explanations of the respiratory murmur as given by Laennec and Beau, some being more favorable to Laennec's explanation; others to that of Beau.

[1]Monrovia, California.

Skoda (8) accepts the cause of the vesicular and bronchial murmur as given by Laennec.

Musser (9), in discussing the bronchial murmur, states: "The sound is caused by the passage of the air through the nares into the wider pharynx when the mouth is closed, and through the trachea and large bronchial tubes;" and states:

"The vesicular murmur is produced partly in the finest bronchial tubes and air cells by their expansion and contraction, and partly in the upper air passages, the latter sound being modified on account of the intervention of the air-vesicles between the ear and the larger bronchi."

Guttmann (10) discusses the theory of Beau that the respiratory murmur is due to the sound made by the air passing through the larynx, the bronchi, and air cells, and says that this theory must give way to Laennec's idea that the sound is produced by the air passing through and dilating the bronchi and then the air cells.

Da Costa (11) believes that the pulmonary tissue is the principal factor. In discussing the theories of the respiratory murmur arising in the larynx and being transmitted down through the bronchi and air cells, and the theory of Sahli that the local movements of the pulmonary parenchyma account for certain elements in the murmur, he states: "Together these two hypotheses serve as a better explanation than the original theory of Laennec that the sound was due to the friction of the air current in the bronchi and infundibula."

Powell and Hartley (12) state: "Laennec was of the opinion that the sounds originated in the affected lung, but it is now admitted that they are in reality generated in the larynx, and thence conducted down the passages into the chest, and so to the observer's ear."

Elmer and Rose (13) are dissatisfied with both Laennec's and Beau's suggestion for the cause of the respiratory murmur and state that the "vesicular murmur is merely bronchial breathing softened in its transmission from the larynx along the aerial column contained in the trachea and bronchi, mingled with the soft crepitation of innumerable pulmonary alveoli during their inflation and subsequent collapse."

It will be seen that none of these authors divorces his idea from the air column and the structures of the upper air passages and the bronchial and pulmonary tissues. All describe the inspiratory murmur as being longer than the expiratory.

These descriptions are not satisfactory, nor are they in accordance with present knowledge. They must be studied further to make them most useful. The physician who practices at the bedside should develop his ability to see, hear, and feel the signs of disease which the patient presents. It is necessary for him to make himself as independent as possible of roentgenographic examination because it is not always available. Any knowledge that will make physical diagnosis more useful is to be desired. The following discussion of auscultation and the respiratory murmur is offered with this in mind.

During the writer's more than fifty years of examining chests, he has made certain observations which are contrary to these teachings and which he believes will make auscultation more useful.

It is evident to anyone who will examine carefully that, normally, inspiration is not longer than expiration—10:2, 5:3, 3:1, et cetera, as taught; but actually shorter.

The weakness of the respiratory murmur in case of abdominal breathing indicates that the air column passing through the larynx and bronchi and expanding the air cells cannot be the origin of the respiratory sounds, for the air enters the

air passages the same as it does in the usual type of breathing, yet the murmur is weak. We also have a respiratory murmur when the larynx is by-passed by the bronchoscope.

Moreover, it is not rational to accept without questioning that the murmur heard near the hilum and in the interscapular region is produced, even chiefly, by the air as it passes the glottis, enters and dilates the bronchi, impinging on their surfaces, and that in the main portion of the lung, by air entering and dilating air cells.

Relation of respiratory murmur to respiratory mechanism: What may we offer as a substitute for these long held opinions? After noting that inspiration is not longer than expiration, the writer was next impressed with the fact that there is a muscular element in the murmur (14). By placing the stethoscope over a contracting biceps, a sound was heard which possessed some of the qualities of the respiratory murmur. It was noted during normal breathing that a fairly good but weak murmur could be heard over the abdominal muscles. A murmur was also noted over the chest wall where the lungs were collapsed by pneumothorax and the lung tissue was separated widely from the chest wall by an air cushion. Such murmurs are usually weak if the pressure is marked, but sometimes, when the parietal pleura is thickened, they may not be far from normal in their intensity, indicating that different factors enter into their production. The thickness of the pleura alters the murmur, sometimes increasing and sometimes decreasing it. More recently a weak respiratory murmur was heard over the chest wall where the lung had been removed by pneumonectomy. Surely the entry of air could not be responsible for this sound because the pulmonary elements with the air current had been removed from the side.

To what can the sounds be attributed in pneumothorax and pneumonectomy, where a little air may enter in the one case, and none in the other? On careful analysis the answer seems evident. The respiratory murmur begins with the inspiratory movement and ends with the adjustment of the pulmonary tissues at the end of the expiratory movement. Is it not reasonable then to attribute the murmur to the respiratory mechanism, every part that causes and transmits sound vibrations; the muscles, the bony cage, the pleura when inflamed or thickened, the mediastinum especially when pathological, the bronchi, the pulmonary tissue, the air passages, and the column of air?

It seems rational to look upon the air column and air spaces as incidental rather than the chief factors in the production of the respiratory murmur. The force of the tidal air as it enters the lungs is nullified by the residual air already present, and the air after entering the large bronchi diffuses into the small bronchi and alveoli when the thorax is enlarged and is expressed during the contraction of the thorax.

That part of the respiratory mechanism which is responsible for the *bronchial murmur* is normally limited to the superior portion of the chest and is most distinct posteriorly. Here the sound vibrations are produced by the air current, the larger bronchi, a comparatively small amount of pulmonary tissue, a heavy musculature, and the least elastic portion of the bony cage.

On the other hand, that part of the respiratory mechanism which is largely

responsible for the *vesicular murmur* is dominant in the anterolateral and lower portions of the lungs. Here the murmur is composed of vibrations which originate in structures largely air-containing (the finer bronchi and air cells) plus a limited musculature and an elastic bony cage.

In auscultation of the normal lung and pleura, we are listening to the complex sound caused by vibrations in the respiratory mechanism in action; and in pathological conditions, we hear that modification of the normal sounds which the particular pathological process causes in the action of the respiratory mechanism. No other explanation seems adequate to account for the variations in the respiratory murmur which are met in diseases of the lungs and pleura. Infiltration decreases the proportion of air-containing elements, which produce sound vibration, and disturbs the action of the respiratory mechanism.

Moreover, in the sounds heard on auscultation it is evident that there are two distinct factors which must be taken into consideration: sound production and sound transmission. Sometimes one is predominant, and again, the other. The respiratory murmur heard at any given point consists of a composite sound originating in that portion of the respiratory mechanism which is transmitted to the ear at the point of observation.

Infiltrations in the lung alter respiratory movement and, according to their nature, size, density and location, change the sounds. They act in two ways:

First, acute inflammatory processes such as active tuberculosis cause spasm of apical muscles, particularly the sternocleidomastoid, scaleni, levator anguli scapulae and acromial portion of the trapezius above, and the crus and central tendon of the diaphragm below, and modify respiration by reflexly lessening the movement of the hemithorax in which the pathological process is located (15, 16, 17).

Second, all infiltrations, whether inflammatory or noninflammatory, interfere with full respiratory movement by their presence, the amount of interference varying with the extent and character of the infiltration. They also modify sound transmission.

It readily can be seen that the effect of both the reflex and the infiltration *per se* is to slow and lessen both the inspiratory and expiratory movement. This alters the sound vibrations. It prolongs both phases of the respiratory murmur and in many instances produces a higher-pitched note. If the infiltration results in much fibrosis, then the murmur may show the above disturbances to a high degree and be transmitted with increased force. This we see in the increased voice transmission caused by extensive scar tissue in tuberculosis, particularly when situated near the apex; or in a cavity with smooth walls surrounded by dense scar tissue—the *pectoriloquy* of Laennec.

The respiratory murmur may have different qualities according to the individual chest, the part of the chest in which the infiltration is located, and the particular characteristics of the infiltration. All of these factors will influence respiratory movement differently. One rarely finds a markedly harsh murmur or marked voice transmission when the infiltration is small, scattered, or situated deep in the lung, surrounded on all sides by functioning pulmonary tissue, no matter what the characteristics of the pathologic process. If the infiltration is small, the

respiratory mechanism may be influenced so little that the presence of the pathology may be wholly overlooked on auscultation.

Emphysema, such as we find in chronic bronchitis, bronchiectasis, asthma, or the compensatory emphysema found in chronic, far advanced tuberculosis, changes the respiratory movement and the accompanying murmur according to the following pattern which varies according to the degree of emphysema present: The lungs at rest are dilated; the intercostal spaces are distended; the bony cage is fixed and rigid; and the diaphragm is depressed and incapable of full movement. Every factor which enters into normal respiratory movement is limited in its activity, hence the respiratory murmur is weak.

In pneumothorax, the auscultatory sounds consist partly of the weak contraction of the chest muscles and those made by the feeble movements of the bony cage, plus whatever pulmonary tissue there is to engage in the respiratory movement. In pneumonectomy the stretching of the tissues which occupy the former lung space in response to respiratory effort may produce detectable sound vibrations.

In a chronically contracted lung the pulmonary, the muscular, and the bony cage elements of the respiratory murmur may or may not be largely removed and the sounds vary accordingly. But if there is marked fibrosis or a cavity in the midst of dense scar and the air freely enters, the vocal sounds may be strongly transmitted. This is *bronchophony* and *pectoriloquy*, in which transmission greatly overshadows sound production.

Diseases of the pleura may also alter the respiratory movement and change the respiratory murmur. Acute pleuritis causes local spasm of the intercostal muscles and reduces the movement of that segment of the bony cage over the part of the pleura which is inflamed, causing a decrease in the intensity of the murmur. It also may cause a friction rub when the inflamed surfaces move on each other. Should an effusion occur, the nature of the sounds will depend on the amount of fluid present. Much fluid distends the intercostal spaces, reduces the movement of the muscles and bony cage, separates the pulmonary tissue from the parietal pleura, and lessens the respiratory sounds.

Rales and the respiratory mechanism: Rales may be heard in pathological conditions of both the lungs and pleura. They are called *crepitant*, *subcrepitant*, *gurgling*, and *musical*. Roughly speaking, the first three varieties are considered to be caused by mucus in the bronchi, air cells, and cavities, while the musical rale is an obstructive rale caused by partial blocking of a bronchus. But there are pleural rales which cannot be distinguished from nonmusical rales of pulmonary origin.

The writer knows of no sure way to differentiate the fine and moderately coarse rales originating in the lung from those originating in the pleura. Both may be heard on deep inspiration and on expiration followed by cough and a quick inspiration; and both may now and then be heard on both inspiration and expiration.

The best evidence for differentiating these rales depends on the pulmonary and pleural reflexes; and this is not wholly satisfactory.

If atrophy of the subcutaneous tissue is present and does not extend below

the second rib anteriorly and the spine of the scapula posteriorly, rales heard are most likely of pulmonary origin, because this is the area of the pulmonary trophic reflex.

If atrophy is found anywhere between the second rib anteriorly and the spine of the scapula posteriorly above, and the lower margin of the ribs, this shows that the pleura has been inflamed and as a result the intercostal (18) and subcutaneous tissues (3) are degenerated and rales heard over these areas are likely to be of pleural origin. The fact that sometimes rales are not heard does not mean that no pathology is present.

When the trophic reflex extends from the apex down below the second rib anteriorly and the spine of the scapula posteriorly, rales are uncertain as to origin, for this indicates that both pulmonary and pleural tissues have been involved.

After inflammation of the pleura has subsided, or an effusion has become absorbed, the overlying intercostal and subcutaneous tissues may be permanently degenerated and alteration of the respiratory movement and murmur may persist. Degeneration of the subcutaneous and intercostal tissues with alteration of the murmur frequently follows the thickening of the parietal pleura caused by the irritation of the air in case of pneumothorax treatment. In some of these cases, rales are found and occasionally pain is present. Detectable atrophy is nearly always present if the pneumothorax has been maintained for more than a few months.

Rales arising in both the pulmonary tissues and the pleura may be persistent, and pleural rales may be permanent. I have heard these rales on re-examining patients nearly fifty years after I first noticed them.

It is not at all uncommon for the movement of the chest wall, hence the respiratory murmur, to be perceptibly lessened if the previous pleural involvement was extensive.

Pain may recur years after the acute phase of the pleurisy has passed, especially under conditions of low energy, tiring, emotional stress, worry and disappointment, menstruation, and changes in weather.

Constructive suggestions: This discussion of auscultation is not wholly destructive. There is a constructive side. It attempts to show what the respiratory murmur is not, and also what it is. This discussion takes away much of the independent value heretofore ascribed to auscultation and shows that all methods of physical examination of the lungs and pleura are interdependent. It raises auscultation from its dependence on the erroneous belief that the respiratory murmur is caused by the rush of air into the bronchi and air cells, and gives as its basis vibrations arising in the respiratory mechanism.

With this new conception the so-called *vesicular murmur* is heard in the anterosuperior, lateral, and lower portion of the lung, where the pulmonary tissues are dominant in the production of sound vibrations; and the so-called *bronchial murmur*, in the hilar area and the posterosuperior portion, where the nonpulmonary tissues are dominant, as has long been taught. Infiltrations, no matter where located, reduce the dominance of the vibrations from the pulmonary tissues and make the sounds take on what Laennec called a *bronchial* quality.

The terms *bronchial* and *vesicular* may be retained but they should be assigned to the entire respiratory mechanism and carry the new meaning of dominance in non-air-containing tissues in the production and transmission of the *bronchial murmur*, and dominance in the air-containing tissues in the *vesicular murmur*.

By carefully inspecting and palpating chests, the examiner may determine with fair definiteness how the respiratory mechanism is disturbed. He should pay due regard to the reflex spasms and degenerations caused by pathological changes in both lungs and pleura, and also note the effect on both the form and movement of the chest caused by infiltration and other pathological changes. Prominent among these are emphysema, rigid thorax, and marked contraction, which are often evident to the eye and more fully determined by palpation and percussion. If he will make these initial observations he will have some idea of what the respiratory murmur may be before putting a stethoscope on the chest. However, he must not expect to find the same sounds caused by the same pathology in all chests. We have been taught to expect to find far greater changes in the murmur than are present, especially where infiltrations are small or widely scattered. It is surprising to find how often they are so slight as to be almost unrecognizable.

The examiner must make more of physical examination of the chest than the use of auscultation and percussion. It must mean a complete and careful study of the patient's respiratory mechanism. Seeing and feeling are of equal importance to hearing. Disturbed physiology, as shown in the reflexes and in interference with the respiratory mechanism, which may be determined by inspection and palpation, take on added importance and must be utilized in order to obtain a full picture of any disease affecting either the lungs or pleura. Physical examination must be rewritten with due emphasis on the utilization of all data obtained on sight, touch, and hearing, rather than limiting it to what is heard through the stethoscope and determined by the use of the percussing finger.

SUMMARY

The respiratory murmur cannot be due to the air rushing through the larynx and impinging on the bronchial walls and dilating the air cells, because the lungs always contain residual air which stops the force of the incoming current and causes the air to enter the finer bronchi and air cells by diffusion.

The respiratory murmur consists of a mixture of sound vibrations originating in all components of the respiratory mechanism.

The sound vibrations which cause the *vesicular murmur* originate in the respiratory mechanism in the anterior, lateral, and lower portions of the chest where the air cells predominate, the musculature is light, and the bony cage elastic.

That part of the respiratory mechanism which normally causes the *bronchial murmur* is found in the superior portion of the chest and is most distinct posteriorly. Here the sound vibrations are produced by the air current, the larger bronchi, a comparatively small amount of pulmonary tissue and air cells, a heavy musculature, and the least elastic portion of the bony cage.

The importance of the trophic reflexes in the differentiation of pulmonary and pleural rales is discussed.

One should begin examination by inspection and palpation. By these measures he determines the shape, deformities, and movements of the chest, and whether or not any reflexes or any departures from the normal are present. With this information he may proceed to percussion and auscultation more intelligently and with greater confidence and understanding.

SUMARIO

La Auscultación. Nuevo Concepto del Soplo Respiratorio y de su Puesto en el Diagnóstico

El soplo respiratorio no puede deberse al rápido paso del aire por la laringe, chocando después contra las paredes bronquiales y dilatando las células aéreas, porque los pulmones contienen siempre aire residual que atenúa la fuerza de la corriente de entrada y hace que el aire penetre por difusión en los bronquios más delicados y en las células aéreas.

El soplo respiratorio consta de una mezcla de vibraciones sonoras procedentes de todas las partes componentes del mecanismo de la respiración.

Las vibraciones que ocasionan el *soplo vesicular* tienen su origen en el mecanismo respiratorio de las porciones anterior, lateral e inferior del tórax en las que predominan las células aéreas, la musculatura es liviana y la caja ósea elástica.

La porción del mecanismo respiratorio que ocasiona normalmente el *soplo bronquial* radica en la porción superior del tórax, hallándose más en evidencia en la región posterior, y produciendo allí las vibraciones sonoras, la corriente de aire, los bronquios mayores, una proporción, comparativamente pequeña, de tejido pulmonar, una musculatura pesada y la porción menos elástica de la caja ósea.

Discútese la importancia que revisten los reflejos tróficos en la diferenciación de los estertores pulmonares y pleurales.

El examen debe comenzar con la inspección y la palpación, que permiten determinar la conformación, deformidades y movimientos del tórax y si existen reflejos o desviaciones de lo normal. Con esta información, puede pasarse entonces a la percusión y la auscultación en forma más inteligente y con mayor confianza y comprensión.

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Case Reports

TREATMENT OF ACUTE OBSTRUCTIVE TUBERCULOUS ENTEROCOLITIS BY "NONSURGICAL ILEOSTOMY" AND STREPTOMYCIN[1,2]

A Case Report

JOHN W. WOODBURY AND SAMUEL PHILLIPS

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Although acute obstruction is considered to be a rare complication of tuberculous enterocolitis (1), it is one of the most serious (2). When it occurs, effective treatment is often impossible (1). The following case report includes several unusual aspects but is primarily presented to illustrate a successful method of treating this complication.

CASE REPORT

L. L. C., a 23-year-old white male veteran, first came under our care because of acute tuberculous tonsillitis. The patient had become permanently and totally paraplegic with a "sensory level" at D 5 when his spine and left chest were traversed by a rifle bullet in 1945. He had received surgical, genitourinary and paraplegic attention, and plastic surgery, not as yet completed, for the closure of decubitus ulcers. He was in good nutritional state and free of significant genitourinary infection.

On December 7, 1946, this patient developed a sore throat, followed by nausea, vomiting, diarrhea, severe toxicity, and irregular fever up to 103°F. His tonsils were enlarged and acutely inflamed and within five days exhibited areas of ulceration covered with greyish exudate. There was no significant cervical adenopathy. The patient was investigated and treated energetically with sulfonamides and penicillin without response. In the middle of January 1947, repeated smears from the tonsils showed acid-fast bacilli, subsequently found by culture and animal inoculation to be virulent human tubercle bacilli. Several specimens of sputum and a single stool were also positive for these microorganisms. Chest roentgenograms revealed merely the residual scarring from his old gun-shot wound (figure 1). The patient was given streptomycin, 0.4 Gm. intramuscularly every four hours for seven days and made a very prompt and dramatic recovery.

The sputum, however, remained positive for acid-fast bacilli on smear through March 1947, and even thereafter was intermittently positive for *M. tuberculosis* on culture. Bronchoscopy was performed in April but failed to reveal any tracheobronchial disease. The patient was kept on bed rest and he appeared clinically to be doing well except for occasional brief episodes of diarrhea and low-grade fever, which are not uncommon in most paraplegics. In November 1947, his diarrhea became persistent and the stools exceedingly foul. Hyperpyrexia and leukocytosis were present. The stools were consistently positive on smear and culture for tubercle bacilli. Physical examination at this time revealed that the colon was palpable as an indurated tube from cecum to sigmoid. An ulcerated, macerated, granulomatous mass involving the posterior segment of the anus was also found. Proctoscopy revealed that this mass extended 3 to 4 cm. up the posterior wall of the rectum. Biopsy was taken and revealed tuberculous granulation tissue.

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[1] From the Tuberculosis Section Medical Service, Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis 15, Tennessee.

[2] Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

Upper gastrointestinal series and small intestinal roentgenograms were reported negative. A barium enema on December 10, 1947 demonstrated gross alterations of the colon from the cecum to splenic flexure, with loss of flexibility, reduction of lumen, and irregular gyrated borders of the barium column (figure 2). The cecum appeared most involved. Similar changes were apparent in the last 12 inches of the terminal ileum.

On December 16, 1947, 0.5 Gm. of streptomycin twice daily was started, at first orally. Because there was no apparent effect on either the patient's fever, foul-smelling diarrhea, or general condition, the oral route was discontinued on December 31, 1947 and replaced by 0.5 Gm. of streptomycin twice daily by the intramuscular route which was continued for a total of 120 days.

FIG. 1. Chest roentgenogram November 7, 1947 at time of onset of gastrointestinal symptoms. No evidence of active tuberculosis.

On January 2, 1948 the patient suddenly developed acute lower bowel obstruction with right lower quadrant cramp-like pain, abdominal distension, nausea, and vomiting which soon became fecal in character. Relief was afforded quite promptly by Wangensteen drainage of the stomach and the use of parenteral fluids. During January 1948, however, on five separate occasions there occurred similar episodes of obstruction. All were treated in the same fashion with the result that the patient would retain liquid foods and be able to pass feces normally for three to seven days before obstruction would occur.

In spite of the utmost efforts to maintain the patient's nutrition and the employment of intravenous glucose and protein hydrolysates, the patient's weight dropped from 126 pounds to 112 in thirty days. Consultation with the surgeons confirmed the opinion of all concerned that in the presence of such widespread tuberculous enterocolitis, surgical intervention was inadvisable.

On February 4, 1948 a Miller-Abbott tube was passed down to the distal portion of the ileum and a constant Wangensteen suction was maintained for fourteen days (figure 3). The patient was fed a low-residue liquid diet by mouth with a few low-residue solids, supplemented by a quart of high caloric milk formula per day.[2] This regimen was designed to maintain the patient's caloric and protein requirements by normal alimentation. At the same time it was hoped to prevent further episodes of obstruction by diverting the fecal stream from the terminal ileum back up through the Miller-Abbott tube by means of the Wangensteen suction. Consultation with our gastroenterologist for his opinion of the

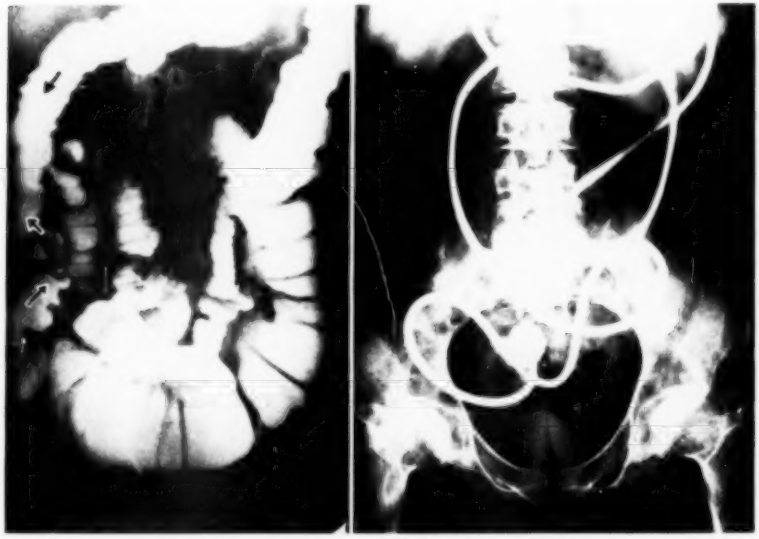

FIG. 2. (Left) Barium enema, December 10, 1947 showing marked involvement of ileum (lower arrow), ileocecal area (middle arrow) and ascending and transverse colon (upper arrow).

FIG. 3. (Right) Miller-Abbott tube within the ileum.

method led to our discovery that a report had just been published by Machella and Miller (3) on the use of the Miller-Abbott tube for similar purpose in the treatment of idiopathic ulcerative colitis. They had termed the method "Medical Ileostomy."

[2] Formula employed:

INGREDIENTS		MEASURE	C	P	F	CALORIES
Skim milk	500 cc.	1 pt.	25	17	1	180
Powdered skim milk	200 Gm.	2 c.	106	72	2	718
Karo	100 Gm.	½ c.	73	—	—	292
Eggs		2	—	14	12	164
Lactose	100 Gm.	1 c.	100	—	—	400
Milk	250 cc.	½ pt.	12	8	10	170
Chocolate syrup	100 Gm.	½ c.	70	0.6	5	321
Total (approximate)	1140 cc.	38 oz.	386	111.6	30	2,245

In our patient 200 to 2,000 cc. of liquid fecal material was obtained daily through the Miller-Abbott tube. The patient was perfectly comfortable during this period and there was no recurrence of symptoms of obstruction. Four days after withdrawal of the tube, however,

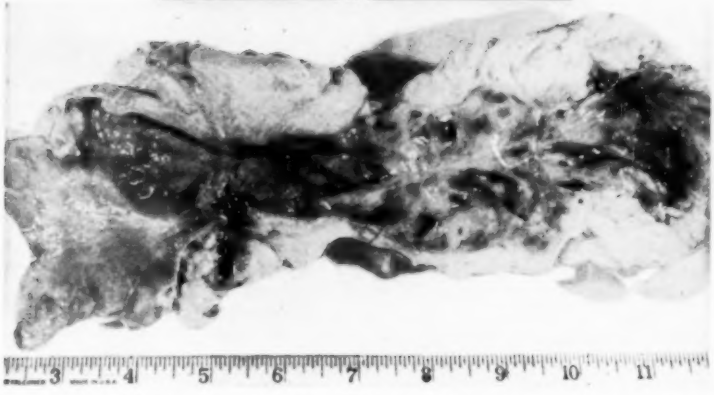

FIG. 4. (Top) Barium enema, April 23, 1948 following conclusion of therapy. The ileum appears improved although markedly dilated (lower arrow). The involved ascending and transverse colon has regained normal appearance (upper arrow). In between is the residual deformity and marked constriction in the barely visible cecum (middle arrow).

FIG. 5. (Bottom) Autopsy specimen of cecum, showing marked fibrosis and constriction.

symptoms reappeared, necessitating the reinsertion of the tube for another period of fourteen days. When the tube was finally withdrawn on March 8, 1948 there was no further clinical obstruction. During the month in which the patient had remained on the described

regimen, he regained 9 pounds of the weight he had lost. He was then able to take a high caloric low-residue diet without difficulty and by April 27, 1948 his weight had increased to 137 pounds, representing a 25-pound weight gain and the best weight he had been able to attain since he had become paraplegic.

In the meantime, intramuscular streptomycin therapy had been continued with disappearance of fever and diarrhea. At cessation of this therapy, the rectal granulomatous mass had shrunk to 2 cm., and a barium enema performed at this time demonstrated marked improvement of terminal ileum and transverse colon with return of normal mucosal pattern, mobility, and flexibility (figure 4). The cecum and ascending colon still showed gross changes with marked stenosis of the lumen immediately above the cecum to a diameter of 5 mm. The stools were still positive for tubercle bacilli and these were found to be resistant to streptomycin.

The question of surgery arose at this time. It was the opinion of the surgeons that because of the very recent widespread involvement of the colon, resection (4, 5) of the residual constricted portion would not be without hazard of reactivation. They also felt that, since the patient was improving so remarkably on the medical regimen, there was no urgency and that it would be wise to wait until a definite period of stability had been attained.

The patient continued to improve in every way until approximately three months after conclusion of the course of streptomycin and more than four months after the withdrawal of the Miller-Abbott tube. On July 20, 1948 he complained of headache. It soon became only too obvious that the patient had developed tuberculous meningitis. The cerebrospinal fluid was under increased pressure, contained 124 leukocytes with 90 per cent lymphocytes, and the values for sugar and chlorides were low. He went downhill very rapidly and expired August 9, 1948.

Gross findings at autopsy showed the ileocecal area to be a mass of cicatricial tissue, in which the appendix was incorporated. The ileocecal junction was so constricted that it would allow the passage of only a thin probe (figure 5). The mucosa of the cecum in this area was red, thickened, and showed several elliptical areas of ulceration measuring 0.2 to 0.5 cm. in longest diameter. The rest of the bowel and the regional mesenteric nodes appeared normal.

The lungs, in spite of a very careful examination, revealed merely a discrete caseocalcific nodule, 1.0 cm. in diameter, at the extreme right apex, and a similar nodule, 0.5 cm. in diameter, in the region of the right hilum. The tracheobronchial nodes appeared normal.

The tonsils were removed and appeared normal on gross examination. Unfortunately, they were lost before they could be examined by microscopic section. The remaining abdominal viscera showed no evidence of tuberculosis. Permission for examination of the brain could not be obtained. However, a portion of the cervical area of the spinal cord was removed.

Microscopic examination of the lungs was negative except for some patchy areas of atelectasis. The spinal cord showed the subarachnoid space to be filled by an exudate of fibrin, and collections of epithelioid and chronic inflammatory cells, involving the pia and blood vessels. The sections from the ileocecal region showed the epithelial lining of the mucosa to be denuded, with some glandular crypts remaining. The tunica propria was thickened by fibrosis and chronic inflammatory cells. The submucosa showed dense fibrosis and chronic inflammation. Scattered throughout the muscularis and serosa were a number of characteristic tubercles.

Although tuberculous enterocolitis is usually associated with progressive, far advanced pulmonary tuberculosis (6, 7), cases of so-called "primary" involvement, where no active pulmonary lesion is present, are described (1, 5, 8, 9). A distinctive feature in this case was that the presence of tuberculosis first became manifest through the development of acute tuberculous tonsillitis. The late recognition of the enterocolitis was undoubtedly related to the patient's paraplegia.

This case demonstrates the relief of obstruction and the maintenance of a patient's nutrition at optimal levels by the use of "nonsurgical ileostomy." By the same means, time was made available for marked resolution of the underlying tuberculous disease by streptomycin. Whether excision of the ileocecal area would have been possible if the patient had not subsequently developed meningitis was not, of course, answered. From the appearance of the bowel at autopsy, however, it was believed that such surgery would have become possible.

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A CASE OF MASSIVE HEMOTHORAX COMPLICATING THERAPEUTIC PNEUMOTHORAX

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REVIEW OF LITERATURE

Hemothorax and hemopneumothorax have occasioned much interest recently because of their frequent occurrence as a result of chest injuries received during World War II. The chief complication to be feared was found to be that of fibrothorax. T. Simpson (1) and A. F. Jonas (2), in their series of cases, advise early aspiration and re-expansion, the latter author having performed thoracotomy with evacuation of the clot and decortication in 38 cases to prevent this development.

The spontaneous occurrence of hemothorax and hemopneumothorax is also not unusual. Two of the earliest reports were those of fatal hemopneumothorax cases described in 1900 by Rolleston (3) and Pitt (4). In the former, sixty ounces of blood were found post mortem in the intrapleural space and no source of hemorrhage could be located. In the latter, there were eight pints of unclotted blood in the pleural cavity while near the apex was an emphysematous bulla attached to which was a torn fibrous band. However, again no patent vessel could be found. There was no evidence of tuberculosis in either case. During subsequent years numerous other cases have been reported. In 1937,. H.U. Hopkins (5) summarized the literature concerning hemothorax, which included 46 cases, and added 3 of his own. This included 4 patients with artificial pneumothorax in whom intrapleural hemorrhage had occurred. One of the latter was that described by Heise and Kraus (6) in 1920 and will be referred to again later. E. Korol (7), in his article on hemopneumothorax and hemorrhagic pleurisy, includes 130 cases, 30 of which occurred during artificial pneumothorax therapy, but he does not distinguish between frank blood and merely blood-tinged fluid. Jones and Gilbert (8) also discuss spontaneous hemopneumotorax and add a case of their own in which death occurred from circulatory obstruction, autopsy disclosing a thick layer of fibrin on both lung and pleura. There were 4,000 cc. of blood and 750 cc. of free fibrin in the pleural space and marked dilatation of the inferior vena cava and the renal and portal veins. The cause in this case was an emphysematous bleb, but the actual site of the hemorrhage was not found.

Subsequent reports include those of Bernstein, Klosk, and Parsonnet (9), A. F. Jennings (10), and Payn and Lief (11). A case of spontaneous hemopneumothorax was also treated at the Kingston Veterans Hospital with repeated aspirations and subsequent re-expansion of the lung. There was no evidence of parenchymal disease.

Hemothorax occurring during the course of artificial pneumothorax must be a rare condition. The case described by Heise and Kraus (6) in 1920 followed the initial refill in a far advanced case of tuberculosis, and the patient died fourteen hours after the onset of symptoms. Autopsy disclosed 2,000 cc. of blood in the pleural cavity; a small hole overlying a cavity and situated near a thick adhesion was apparently the site of the bleeding vessel, but no actual bleeding point could be found. The lung itself was caseous throughout, with numerous cavities. W. L. Meyer (12) describes a case believed to be a consequence of damage to the intercostal vessels during a refill. A total of about 2,100 cc. of

[1] From the Kingston Veterans Hospital, Department of Veterans Affairs, Kingston, Ontario, Canada.

blood were aspirated (1,700 cc. on one occasion) from the pleural cavity in this case. Subsequent progress was satisfactory and the pneumothorax was continued. Other than this latter report, no cases could be found in the literature of recent years. As mentioned earlier, H. U. Hopkins (5) refers to 3 other similar cases and E. Korol (7) to 30 cases, but neither states in how many there was frank hemorrhage. The reports of these cases were not available for further information. C. B. Hogg (13) refers to the puncture of a large vessel occurring during artificial pneumothorax and Parfitt and Crombie (14) also describe a similar occurrence, but in neither case was there the resultant complication of hemothorax.

CASE REPORT

J. L., a 25-year-old ex-private, was admitted to the Kingston Veterans Hospital on February 6, 1946. A left-sided chest pain of one week's duration was followed by a gross hemoptysis of approximately 120 cc. twenty-four hours prior to admission. Physical examination revealed no abnormalities. On a chest roentgenogram a 2.0 cm. cavity opposite the third rib on the left in the region of the hilum could be seen. This contained a fluid level. The lesion had been less prominent but overlooked in the discharge film taken January 9, 1946. Sputum was positive for acid-fast bacilli on direct smear. The erythrocyte sedimentation rate was 11 mm. in one hour.

Because of roentgenographic evidence of cavity closure and temporary "conversion" of sputum, artificial pneumothorax was not commenced until September 13, 1946, when a sputum specimen of July 1946 was reported positive for *M. tuberculosis* following eight weeks' culture. Subsequent progress was uneventful until the night of November 26, 1946. Fluoroscopic and roentgenographic examinations disclosed a satisfactory pneumothorax. A film taken October 30, showed a 50 to 60 per cent degree of collapse following a refill and no adhesions were evident (figure 1). Refills were being given at seven-day intervals and pressure readings were satisfactory; the initial reading averaging −7 −4 and the final reading averaging −3 −0 cm. of water.

On the morning of November 26, the usual refill of 500 cc. was given. The initial reading was −6 −3 and the final −3 −0 in cm. of water. Fluoroscopic examination revealed a 70 per cent degree of collapse and no fluid was present. At about 6 p.m. the same day, the patient complained of slight tightness in the chest. There was possibly a slightly greater degree of collapse but nothing unusual was noted. At bedtime there was only slight discomfort. At midnight he began to hiccough and slept only sporadically. At 9 a.m. he was acutely short of breath, pale, and most distressed because of severe and constant hiccoughing, which had apparently only recently become severe. Fluoroscopic examination revealed marked shifting of the heart and mediastinum towards the right; the collapse now amounted to 80 to 85 per cent, and a small amount of fluid obliterated the costophrenic angle. The intrapleural pressure reading was greater than the height of the manometer scale, *i.e.*, greater than 20 cm. of water positive pressure. Seven hundred cubic centimeters of air were removed and the final reading thereafter was −6 + 1. The procedure was followed by marked relief. Four hours later the dyspnea and hiccoughing returned and 500 cc. of air were aspirated. The initial reading was +5 +10 and again the patient was relieved. Suddenly, about 5 p.m., marked shock, pallor, and cyanosis developed, with profuse sweating and tachycardia. Nausea and vomiting were also severe. The dyspnea was not so marked as previously. The possibility of hemorrhage was immediately considered. Physical examination of the chest revealed flatness posteriorly and there was marked shifting of the mediastinum to the right, the heart sounds only being heard to the right of the sternum. Diagnostic aspiration was productive of blood, the hemoglobin level of the peripheral blood had fallen to 10 Gm. per 100 cc. and a portable roentgenogram of the chest disclosed the fluid level to be opposite the sixth dorsal vertebra. The blood pressure (mm. of mercury) was 90 systolic, 70 diastolic. The clinical evidence of shock rapidly grew more severe. It

was obvious that further hemorrhage was occurring and that urgent measures were necessary to save his life.

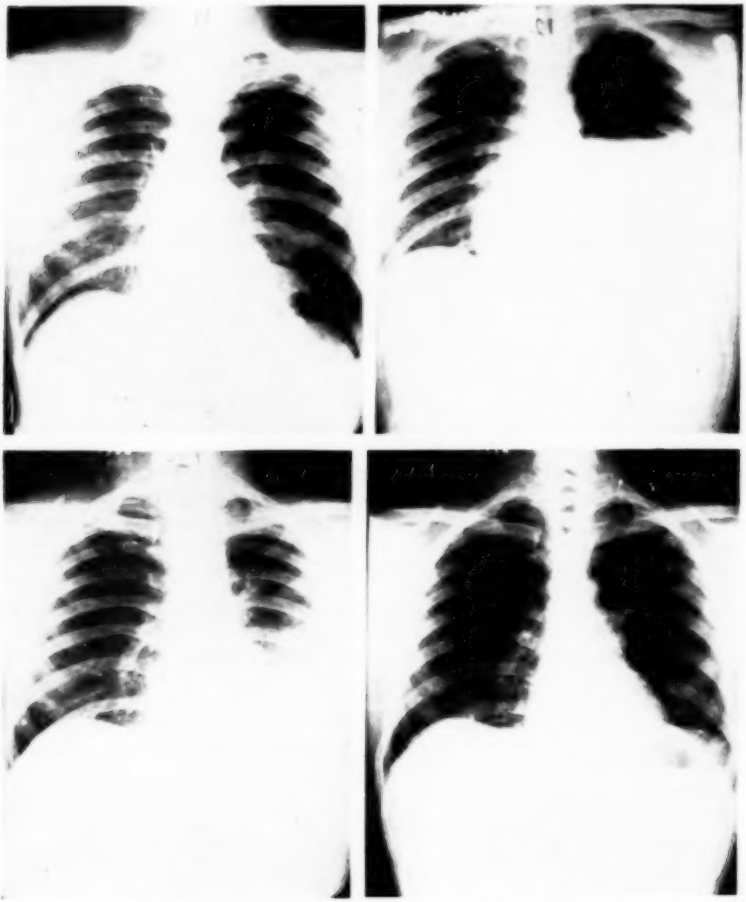

FIG. 1. (Upper left) Roentgenogram of the chest one month before massive hemorrhage into the pneumothorax space. No adhesion visualized.

FIG. 2. (Upper right) Roentgenogram of the chest on the day after hemorrhage showing fluid level and marked shift of mediastinal structures.

FIG. 3. (Lower left) Roentgenogram of the chest five weeks after hemorrhage, showing complete re-expansion of the lung. Pleural clouding still evident.

FIG. 4. (Lower right) Roentgenogram of the chest five months after hemorrhage. There is almost no residual pleural change.

The immediate treatment consisted of the following procedures:

Blood was obtained from the blood bank; in the meantime, 500 cc. of normal saline were administered. The patient was then given four transfusions of 400 cc., 300 cc., 425 cc., and

400 cc. of whole blood (a total of 1,525 cc. during the night), as well as 100 cc. of 10 per cent glucose in distilled water. At 10 p.m. a second portable film disclosed no change in the fluid level and it was decided that the hemorrhage had probably ceased. The clinical condition had also improved somewhat, although shock was still quite pronounced. Blood pressure was 90 systolic, 70 diastolic. By 11:45 p.m., however, there was a distinct improvement and the blood pressure was now 106 systolic, 80 diastolic. The hemoglobin level had risen to 12 Gm. per 100 cc.

On the following morning, the patient was much better and the hemoglobin level was 13.5 Gm. per 100 cc. An aspiration was carried out in the eighth interspace at the midaxillary line and 1,300 cc. of dark red blood were aspirated without difficulty. The patient felt more comfortable and finally became free of nausea and vomiting, so that the intravenous administration of fluids was discontinued. The fluid level in the chest remained about the same, but the heart sounds could now be heard to the left of the sternum. A portable film confirmed the shift of the mediastinal structures, and disclosed the fluid level at the height of the seventh dorsal vertebra as compared with the sixth dorsal vertebra level of the film ten hours previously (figure 2). No further blood was removed then for fear of precipitating further hemorrhage.

The patient's subsequent progress was satisfactory. A temporary leukocytosis of 18,000 cells per cu. mm. on the day of the hemorrhage had decreased to 10,500 on the next day. Subsequent leukocyte counts were normal. The erythrocyte sedimentation rate was elevated to 97 mm. on December 1, but dropped to 13 mm. by December 13. A fever of 100° to 102°F. persisted for four days. Penicillin was administered both intramuscularly and intrapleurally.

The results of further aspirations were as follows:

November 27	1,300 cc. bloody fluid
November 28	600 cc. bloody fluid
November 30	500 cc. bloody fluid
December 1	600 cc. bloody fluid
December 2 a.m.	600 cc. bloody fluid
December 2 p.m.	400 cc. bloody fluid
December 3	200 cc. bloody fluid
December 5	150 cc. dark bloody fluid
December 7	150 cc. dark brown fluid
December 10	200 cc. dark serous fluid
December 11	80 cc. dark serous fluid
December 14	0 cc.
December 16	115 cc. dark serous fluid
December 19	135 cc. dark serous fluid
December 21	100 cc. dark brown fluid
December 23	100 cc. dark brown fluid
December 26	45 cc. dark fluid
December 30	65 cc. dark yellow fluid
January 3	0 cc.
Total	5,340 cc.

The heart and mediastinal structures gradually resumed their normal positions, and the lung had undergone full re-expansion by January 3, 1947 (figure 3). The residual pleural clouding decreased steadily thereafter. In the film of April 14, 1947 almost no pleural changes can be detected (figure 4), while that of October 16, 1947 reveals obliteration of the costophrenic angle as the only finding. The physical findings on examination of the chest have also returned to normal. Fluoroscopy disclosed moderate mobility of the left diaphragmatic dome; successive sputum examinations have been negative for tubercle bacilli on culture, and tomographic series failed to reveal evidence of cavity formation. It is therefore to be hoped that the original parenchymal lesion will remain under control.

COMMENT

The possible sources of the hemorrhage in this patient could have been the following:

(*1*) Puncture of the lung by the pneumothorax needle. This is considered unlikely as there was good collapse before the refill.

(*2*) Injury to the intercostal vessels as in Meyer's (12) case. This is considered to be unlikely because the dyspnea preceded the hemorrhage by some hours.

(*3*) Rupture of a vesicle on the surface of the lung.

(*4*) Tearing of a vascular adhesion.

It is thought that the last named is the most likely explanation in spite of the fact that no adhesion was visualized roentgenographically. In the case described by Heise and Kraus (6), autopsy disclosed a hole in a thinned-out area overlying a cavity and situated near a thick adhesion which had torn. In this case there was no such disease in the lung parenchyma, and the hemorrhage would probably have to be attributed to bleeding from the parietal stump of a torn adhesion.

As to treatment of hemothorax, most authorities are in agreement that following the period of actual hemorrhage the blood should be aspirated as soon as possible to prevent the development of a fibrothorax (1, 2, 5, 6, 7, 8, 9, 10). Though blood does not clot in an uninfected pleural cavity, the fibrin does settle out and may leave a thick shaggy layer on the surface of both lung and parietal pleura.

Therefore, it was decided that the blood from this patient's chest should be aspirated frequently. Also, it was considered that the pneumothorax should be abandoned, as the danger of the development of unexpandable lung with fibrothorax was felt to be so great. Moreover, the possibility of the further occurrence of a hemorrhage which might be even more severe could not be excluded. Thoracoscopic examination might have been considered but it is doubtful if it would have served any useful purpose, and the patient's condition hardly warranted the procedure. Even in several autopsied cases, no actual bleeding point could be definitely located. Penicillin was administered, both intrapleurally and intramuscularly, as it was felt that every precaution against infection should be taken.

SUMMARY

The literature concerning spontaneous hemothorax and hemopneumothorax is reviewed and a case is reported in which a massive hemothorax occurred during the performance of a routine pneumothorax refill.

SUMARIO

Caso de Hemotórax Masivo como Complicación del Neumotórax Terapéutico

Después de repasar la literatura referente al hemotórax y el hemoneumotórax espontáneos, preséntase un caso en el cual cual sobrevino un hemotórax masivo durante la ejecución de una reinsuflación corriente del neumotórax.

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POLYCYTHEMIA SECONDARY TO TUBERCULOSIS OF THE SPLEEN[1, 2]

Report of a Case and Review of the Literature

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An occasional reference is found in the earlier medical literature to a syndrome characterized by tuberculosis of the spleen and polycythemia. No adequate explanation of this relationship has ever been offered.

Tuberculosis of the spleen is arbitrarily spoken of as primary or secondary. Secondary tuberculosis of the spleen is quite common and is frequently found in generalized tuberculosis. Primary tuberculosis of the spleen (a misnomer by modern concepts of the disease, since the spleen cannot be the only or initial focus of tuberculosis) is a term reserved for those cases in which the spleen becomes involved by hematogenous spread and in which the splenic focus enlarges and caseates while the other foci either heal or become quiescent (5, 8, 12, 18, 38). Under this circumstance the spleen becomes the "primary" site for further dissemination. In attempting to classify cases of this type, it is often difficult to decide whether the other tuberculous foci are sufficiently quiescent to permit consideration of the spleen as the primary or superior site.

Review of Literature

One of the most complete reviews of the subject of primary splenic tuberculosis was published by Winternitz in 1912 (44). Of 51 cases summarized, only one showed tuberculosis confined entirely to the spleen. In 40 per cent there was pulmonary tuberculosis, in 57 per cent regional lymph nodes were involved, and in 80 per cent the liver also showed tuberculosis. Sixty-six per cent of those who had tuberculosis of the lungs also had tuberculosis elsewhere. In 1924 Magnac (25) published a monograph on primary tuberculosis of the spleen and collected 19 more cases. Shands (37) was able to collect 80 cases of tuberculosis of the spleen up to 1933, and Englebreth-Holm (10) added 28 more in 1938. More cases have been reported singly since then so that there are now between 100 and 150 published cases in all. Calcification of the spleen, found on roentgenographic or postmortem examination is considered to be tuberculous in origin. Moorman (29) collected 29 cases of splenic tuberculosis with roentgenographic evidence of calcification, but made no distinction between primary and secondary types.

Secondary splenic involvement is not rare. Klotz (22) found tuberculosis in 172 of 404 post-mortem examinations and, of these, 69 had tuberculosis of the spleen. Gohn (13) found involvement of the spleen in 55 out of 125 cases, and in a publication of the South African Institute of Medical Research (39) 51 per cent of the natives dying of pulmonary tuberculosis were reported to have had tuberculosis of the spleen as well. Hoyle and Vaizey (19) found involvement of the spleen in 31 of 110 cases of miliary tuberculosis.

Polycythemia was first described as a definite entity in 1892 by Vaquez (42). In this condition, too, primary and secondary types are recognized. The diagnosis of "primary" or polycythemia "vera" depends on the absence of demonstrable etiology, the presence of an elevated erythrocyte, leukocyte, and platelet count, and an increase in the blood

[1] From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Illinois.

[2] Aided by a grant from the Wilson Laboratories, Chicago, Illinois.

volume. In secondary polycythemia the elevated erythrocyte count occurs in response to increased oxygen demand. In many of the reported cases it is difficult to determine whether the polycythemia is primary or secondary because of insufficient data, this being especially true in cases of the syndrome under discussion. Furthermore, the division between normal and polycythemic levels must, at best, be arbitrarily set. Many of the reported cases have erythrocyte counts definitely in the polycythemia range (7 to 11 million per cu. mm.) while others, with pulmonary or miliary tuberculosis and splenic involvement confirmed by operation or post-mortem examination, had counts but slightly over 5.0 million per cu. mm. Even such elevations of the count, however, are unusual since the rule is for anemia to accompany infections (34, 45), especially such severe ones as miliary tuberculosis.

In the syndrome of polycythemia and tuberculosis of the spleen, the splenic involvement is not always "primary" but may be part of a generalized tuberculosis. In table 1 are listed the reported cases of tuberculosis involving the spleen, both primary and secondary, where erythrocyte counts were over 5.0 million per cu. mm.

Report of Case

At the time of her first hospital admission to the Cook County Hospital, on August 19, 1936, the patient was 23 years old. The diagnosis on admission was "blood dyscrasia with splenic enlargement." Two years before admission, previous to which she had felt quite well, she became ill with "rheumatism," characterized by pain involving the ankles and knees of both feet. These joints became so swollen and tender that she was unable to walk, but after resting for two weeks she felt considerably better. Subsequently she had occasional pain in her feet and knees, without swelling. A year later she began to have frequent sore throats, usually accompanied by fever. She was advised to have a tonsillectomy, but this was indefinitely postponed because of fever. Six days before admission she noted the gradual onset of pain in the left upper quadrant of the abdomen. The pain was aggravated by deep inspiration, radiated to the back, and was described as a sensation of "something catching under the ribs." She had no cough, chills, or fever, but had had night sweats. There was in addition, a history of frequent "boils" under the arms, bleeding from the gums following slight trauma, "sinus pains" on the right side, and weight loss. During the preceding week there was a loss of appetite and almost everything caused dyspepsia.

Physical examination revealed a comfortable Negro female, not acutely ill. Her temperature was 99°F., the blood pressure (in mm. of mercury) was 136 systolic and 78 diastolic. The gums bled easily on pressure. The tonsils were enlarged and red. There were no palpable lymph nodes. The heart was normal. The spleen extended approximately 5.0 cm. below the costal margin, was firm, somewhat tender, and a friction rub was heard over it. The liver was not enlarged. Serologic tests for syphilis (Wasserman, Kahn) were positive. Diphtheroid bacilli were cultured from the throat. The blood findings were as follows: erythrocytes 7.36 million per cu. mm.; concentration of hemoglobin, 85 per cent (Sahli); total leukocytes, 9,700 per cu. mm.; neutrophils, 66; lymphocytes, 28; monocytes 1; and basophils 5 per 100 leukocytes. On August 25, 1936 the values were: erythrocytes, 7.20; concentration of hemoglobin, 110 per cent, total leukocytes, 9,000; neutrophils, 66, lymphocytes 25, monocytes 5 and eosinophils 4 per 100 cells. Roentgenograms of the splenic area failed to outline the spleen or reveal any foci of calcification, while those of the chest showed bilateral increase in the markings at the hilum. Examination of the bone marrow was reported as showing no evidence of leukemia.

Shortly after admission the patient's temperature rose to 100°F. but returned rapidly to normal and remained so for the rest of her hospital stay. On September 2, 1936 she had two teeth extracted and bled from the tooth sockets for two days, in spite of packing. This bleeding finally stopped spontaneously and she was discharged, feeling considerably improved.

On June 8, 1937, she was again admitted to the hospital because of pain in the left upper quadrant of the abdomen and swelling of the ankles accompanied by dyspnea on exertion, present for about eight months. At first the abdominal pain was sharp in character and radiated around to the left side, but for several months it had been intermittent and accompanied by a sensation of fullness in the epigastrium. The pain was not relieved by sodium bicarbonate and at times seemed to be worse after meals. During this period her appetite had been poor and she had lost ten pounds in weight. For three days preceding admission, she had vomited following every meal. Her menstrual periods had become quite irregular.

Examination revealed dilated conjunctival vessels, gums which bled easily, carious teeth, enlarged, red, and cryptic tonsils. There was a slight depression of breath sounds over the left lung but no rales were heard. Examination of the heart revealed no abnormalities except for tachycardia. A bulge was visible in the left upper quadrant of the abdomen which, on palpation, was found to be a firm, tender spleen, the lower pole of which was 5 cm. above the left iliac crest. The liver edge was just palpable. On the lateral aspects of the legs were scattered and tender raised nodules covered with shiny atrophic skin, characteristic of erythema nodosum. There was a distinct copper hue to the skin, especially marked over the nose and malar prominences. Examination of the blood on this admission revealed the following values: erythrocytes, 6.6 million; concentration of hemoglobin, 90 per cent; total leukocytes, 17,000 per cu. mm. with 79 polys, 14 lymphocytes, 2 monocytes, 3 basophils, and 2 eosinophils per 100 leukocytes. Platelets were abundant in the blood film. There was a two plus albuminuria. The concentrations of sugar and uric acid in the blood were 68 and 7 mg. per 100 cc., respectively. Disruption of erythrocytes started at .40 per cent and was complete at .30 per cent saline. Agglutinations for typhoid, paratyphoid A and B, and melitensis were negative. A blood culture was sterile. Pelvic examination revealed nothing abnormal. A roentgenogram of the teeth showed multiple retained-root fragments and abscesses. A retrograde pyelogram showed marked rotation and distortion of the pelvis of the left kidney and defined the abdominal mass as spleen. The bone marrow at this time was reported showing proliferation of granulocytes, with no evidence of leukemia.

On April 19, 1937 the erythrocyte count was 9.15 million per cu. mm. with 126 per cent hemoglobin. The mucous membranes were cyanotic and she began complaining of frequent vomiting. She was given 0.1 Gm. of phenylhydrazine daily, and during the following week 1,000 cc. of blood were withdrawn. The vomiting persisted but the abdominal pain disappeared. A small gastric ulcer was demonstrated at this time on the posterior wall of the stomach close to and just above the incisina angularis.

On May 5, 1937 X-ray therapy to the spleen was started. On May 26, 1937 it was noted that the coppery hue of the skin was gone, the spleen was palpable only 3.0 cm. below the costal margin, her appetite was good, and she did not complain of any digestive disturbances. At the time of her discharge from the hospital, she had 6.45 million erythrocytes per cu. mm., 100 per cent concentration of hemoglobin, and 7,100 leukocytes per cu. mm. She was seen in the outpatient clinic irregularly after this and remained relatively asymptomatic until November 1938 at which time she suddenly vomited large clots of blood.

She was admitted to another hospital where she was found to have an erythrocyte count of 2.0 million per cu. mm. She received blood transfusions, improved gradually, and was discharged feeling well.

On February 9, 1939 she re-entered the hospital with a three-day history of a "cold," cough, frontal headaches, and left upper quadrant pain which was "shooting" in character. On the evening preceding her admission she again vomited blood. She did not have abdominal pain at the time and had felt fairly well since the last episode of hematemesis three months before. She did not appear seriously ill; there was tenderness over the frontal sinuses, the nasal mucous membranes were red and boggy, and the pharyngeal mucosa was granular and infected; the thyroid gland was palpable. There was no significant adenopathy. The lung fields were resonant on percussion and the breath sounds in the hilar region

were harsh. Examination of the heart was normal. The abdomen was flat except for visible fullness in the left upper quadrant due to the firm, nontender spleen which extended to the level of the umbilicus. The liver edge, firm and nontender, was palpable 3.0 cm. below the right costal arch. The deep reflexes were difficult to obtain.

During the next few days her temperature was consistently elevated (102°F. being the highest) and she complained of headaches and tenderness over the frontal area. On transillumination the frontal and right maxillary sinuses were dark. The right antrum was washed and a considerable amount of pus was obtained. Her blood findings were: erythrocytes, 4.88 million per cu. mm.; concentration of hemoglobin, 70 per cent; total leukocytes, 18,650 per cu. mm.; platelets 1,800,000. Roentgenographic examination of the stomach and esophagus failed to reveal varices or ulcers. The stools contained occult blood. The blood sugar was 87 mg. per 100 cc. and the nonprotein nitrogen, 39 mg. per 100 cc. After she had been in the hospital for about two weeks she had a sudden feeling of weakness and again vomited a great quantity of blood, the amount of which was not measured. Following this, the blood pressure dropped to 102 systolic, 60 diastolic, the abdomen remained soft, and there was no evidence of shock. The following day her erythrocyte count was 3.40 million with 42 per cent concentration of hemoglobin, and the blood pressure had risen to 120 systolic, 68 diastolic. She was given intravenous fluids for several days but continued to be nauseated and vomited occasionally. One week later she again vomited about 1,000 cc. of blood. After this the erythrocyte count was 2.65 million and concentration of hemoglobin, 38 per cent. Three days after the last bleeding episode, when her temperature was 104°F., she complained of "girdle pains" and tenderness over the lower ribs posteriorly. The spleen seemed more tender than usually. Her erythrocytes had fallen to 1.91 million per cu. mm. A week later her temperature was still elevated; she was complaining of abdominal pain and had a profuse whitish vaginal discharge in which gram-positive extracellular diplococci were found. There was tenderness over the liver and spleen and in both costophrenic angles. Pelvic examination was negative. A blowing precordial systolic murmur was now noted, but blood cultures and agglutination tests were again negative. The marrow was hypercellular and revealed changes compatible with stimulation due to blood loss. Pain in the left chest, aggravated by respiration and radiating to the left shoulder appeared; the spleen became more tender, and a diagnosis of perisplenitis was entertained.

On the forty-seventh hospital day her abdomen was noted to be distended and tympanitic, there was questionable jaundice, and her temperature was still elevated. The icterus index was 10, the Van den Berg reaction was negative direct, positive indirect. In the next few days fluid began to collect in the abdomen and paracentesis yielded 1,200 cc. of cloudy yellow fluid with a specific gravity of 1.010. A smear was negative for acid-fast bacilli, the test for albumin was four plus and there were 200 leukocytes and 500 erythrocyte cells per cu. mm. On the same day she vomited a large amount of blood. A roentgenogram of the chest showed a clouding in the left base suggestive of pleural effusion. Her erythrocyte count was 2.62 million per cu. mm., hemoglobin concentation, 50 per cent; total leukocytes 8,100, per cu. mm. She was given 350 cc. of blood with no reaction and several days later 250 cc. more. The septic temperature and the vaginal discharge continued unabated. She reaccumulated peritoneal fluid, and was given 500 cc. of blood (followed by a severe chill). The next day she had an erythrocyte count of 2.84 million with 44 per cent concentration of hemoglobin. The platelet count was 410,000 and the leukocyte count, 14,150 per cu. mm. The reticulocyte count was one per cent. Three thousand cubic centimeters of yellow fluid were withdrawn from the abdomen.

Her course was steadily downhill. She continued to complain of cough and pain over the spleen. Her temperature often rose to 104°F. On two other occasions 4,000 and 3,000 cc. of fluid were removed from the abdomen. The congo red test revealed 29 per cent retention in one hour. Her last erythrocyte count was 5.21 million with 70 per cent hemoglobin. The platelet and total leukocyte counts were 230,000 and 13,400, respectively. She continued to grow weaker, became emaciated, and expired 111 days after admission.

At post-mortem examination the peritoneal cavity contained 3,000 cc. of yellowish fluid.

The peritoneal surface was found to be studded with tiny yellowish-grey nodules. The periaortic and mesenteric lymph nodes were much enlarged. The liver weighed 1,200 Gm. On cut section, a biliary radicle in the right lobe was surrounded by a yellowish white area, measuring 3.0 cm. in greatest diameter. The spleen weighed 1,100 Gm. There was increased resistance to cutting and there were several well-demarcated wedge-shaped infarcts. In the parenchyma, 5.0 cm. beneath the capsule, there was an 8.0 cm. circular area of caseation. The kidneys were grossly normal except for an area of caseation in the region of the lower calyx on the left. The tubes and ovaries were closely adherent and bound by multiple serosal adhesions. The heart was essentially normal. The right lung and pleural cavity were free of gross pathological changes, but the latter contained 1,000 cc. of fluid. The left pleural surface was studded with millet-sized nodules and the cavity contained 2,000 cc. of fluid. On cut surface the left upper lobe disclosed a 5.0 cm. caseous focus within its parenchyma while the left lower lobe was the site of extensive caseous pneumonia. The left hilar, tracheobronchial, and mediastinal lymph nodes were enlarged and caseous. Microscopic examination confirmed the presence of disseminated tuberculosis with caseous focal tuberculosis of the left upper lobe, tuberculosis of the hilar, mediastinal, and periaortic lymph nodes. There was a generalized tuberculous peritonitis and a tuberculoma of the left kidney. There was miliary tuberculosis of the Fallopian tubes. There was no evidence of an active peptic ulcer to explain the hematemeses. There were, however, moderately large esophageal varices but no site of previous rupture could be demonstrated. The spleen was made remarkable by the absence of the usual splenic histologic findings. Only an occasional follicle was seen. Innumerable sharply defined, widely-gaping sinusoids engorged with red blood cells were evident. The trabeculae were prominent and the stroma was densely fibrotic. In one region a diffuse organizing tuberculous perisplenitis was in evidence. There was another sharply defined area of tuberculous necrosis in the parenchyma. The areas of infarction were necrotic and surrounded by leukocytes and a zone of hyperemia.

It was felt that this case represented a childhood type of primary pulmonary tuberculosis with secondary miliary dissemination and extensive splenic involvement.

DISCUSSION

The triad of cyanosis, polycythemia, and splenomegaly was suggested by Rosengart (35) as being diagnostic of primary tuberculosis of the spleen. It is now realized however, that this triad is commonplace in polycythemia rubra vera. Abdominal pain, a palpable spleen, or both, characterized tuberculosis of the spleen in 70 per cent of Winternitz's (44) cases. Weakness and loss of weight were also usually present. Winternitz, however, pointed out that these cases may have an onset not unlike an acute infection with collapse, fever, chills, backache, and acute clinical course. The blood picture is inconstant. Blood counts were done in 26 of his 51 cases, and of these 9 were normal, 11 had anemia, and 6 had polycythemia. We were able to find 29 additional cases having erythrocyte counts over 5,000,000 per cu. mm. Fifteen of these were considered to have "primary" tuberculosis of the spleen. Ten of these, plus our own case, can be considered as having significant polycythemia. Head's (14) case of polycythemia with splenomegaly cannot be accepted as secondary to splenic tuberculosis since the only evidence offered is a positive Mantoux test. The combination of tuberculosis, polycythemia, and splenomegaly may be misleading. Leon-Kindberg (21) presented a case with an erythrocyte count of 8.5 million per cu. mm., fibrous pulmonary tuberculosis and a splenomegaly, but post-mortem examination failed to show any evidence of tuberculosis in the spleen.

Cases 8, 16, and 25 can be accepted on fairly good evidence. Zadek's (46) case (No. 25) had a tuberculous iridocyclitis, pulmonary tuberculosis, and a splenomegaly. The patient's first Mantoux test was negative. Subsequent counts were lower, the Mantoux test became positive, and with clinical improvement the spleen became smaller. Mauriquand's

TABLE 1

Summary of Reported Cases of Tuberculosis Involving the Spleen (both Primary and Secondary) in which Total Erythrocyte Counts of over Five Million per cu. mm. Were Recorded

	AGE	SEX	RBC	HGB.	WBC	SPLEEN	SPLENECTOMY	EXTENT OF SPLENIC INVOLVEMENT	PRESENCE OF MILIARY TUBERCULOSIS
1. Barlaro (1)			6.5				no	Not stated.	Probable. Lesions of kidney, bladder and spleen.
2. Bayer (2)	53	M	6.0	40%	7,500	1,750 G.	yes	Myriads of small conglomerate tubercles.	Unknown. Patient recovered after splenectomy. Lungs and liver not grossly involved.
3. Brown, *et al.* (3)	54	M	5.2	14*	1,500	2,700	no	Diffuse small areas of tuberculous necrosis.	Lungs negative, but tuberculosis demonstrated in spleen, liver, nodes, liver hilum, and one paratracheal node.
4. Brunard (4)	7	M	6.0	50%	8,000		no	Not stated.	Probable. Lungs involved; cervical adenitis, ascites.
5. Cominotti (6)	33	F	7.5	80%	6,000	2,250	yes	"Much scarred."	Probable. "Caries of spine" and one small tuberculous nodule in liver.
6. Coyon (7)	56	M	7.9	95%	42,000		no	Spleen huge with large and small tubercles. Microscopic: diffuse caseation	No. Spleen apparently primary site at time of autopsy. No miliary tubercles.
7. Douglas et Eisenbrey (9)	39	M	8.8	120%	23,000	1,350	yes	Diffuse small areas of necrosis. There was one large area of infarction showing complete necrosis.	Yes. Lungs, liver, splenic bed, diaphragm.
8. Forsell (probable)(11)		F	7.2	103%	21,000		no	Calcification noted in spleen on roentgenogram.	Unknown. Patient alive at time of report.
9. Heyman(15)	3		5.58	72%			no	Two identical sized spleens and five smaller ones involved in caseous tuberculosis.	Yes. Lungs, mediastinum, and colon.
	3		5.68	80%			no	"Numerous tubercles in spleen."	Yes. Lungs, meninges, liver, spleen, et cetera
	child		6.6	84%			no	"Extensive tuberculosis of spleen up to pea-sized tubercles."	Yes. Lungs, mediastinum, lymph nodes, meninges, brain, et cetera.
	7†		5.2	92%			no	Not stated—"miliary tuberculosis of spleen."	Yes.
	13†		6.2	67%			no	Not stated—"miliary tuberculosis of spleen."	Yes.

TABLE 1—*Concluded*

	AGE	SEX	RBC	HGB.	WBC	SPLEEN	SPLENECTOMY	EXTENT OF SPLENIC INVOLVEMENT	PRESENCE OF MILIARY TUBERCULOSIS
10. Hickling(16)			5.1	100%	5,300		yes	Splenic tissue almost entirely replaced by tissue showing microscopic features to tuberculosis with typical focal arrangement but without caseation.	Yes. Roentgenographic evidence in lungs.
11. Jedwabnik (20)	49	M	20 mil?	170%	5,000		no	Spleen enlarged. Numerous miliary to pea-sized partly confluent irregularly outlined grey-white foci.	Yes.
12. Lambert et Bottin (23)...	53	F	5.2	80%	1,900		yes	Diffuse	Unknown. Patient recovered after splenectomy.
13. Lederer (24)	49	M	9.7	140%	6,600		no	Capsule studded with pinhead to lentil-sized foci.	Yes. Liver, lungs, kidney.
14. Margolis (26)	57	M	7.00	110%	5,800		no	Spleen very large—changes apparently diffuse.	Not stated.
15. Matzdorff (27)	59	M	5.6	109%	15,000		no	Diffuse	Yes. Both lungs.
16. Mauriquand (probable)(28)	11†		9.2	95%	5,000		no	Not stated. Spleen enlarged.	Probable.
17. Moutard-Martin et Lefas (30)....	49	F	8.20			1,750	no	"Many caseous nodules"	Probable. Calcified nodules in lungs, liver and mesenteric nodes.
18. Pether (31)			5.64	80%	7,500		no	Spleen studded with nodules having central caseation.	Yes. Apices of lungs, brain, stem, kidneys.
19. Rendu et Widal (32)....	40	M	6.20		6,000	3,780	no	Conglomerate tubercles and sclerosis.	Yes. Lungs, liver, kidneys, pancreas.
20. Rennen (33)	67	M	8.80	130%	13,400	1,900	no	Numerous grey and white caseating nodules, pinhead to pea-sized.	Yes. Lungs, liver, kidney and bone marrow.
21. Sachs (36)	58	M	11.00	150%	25,000	700	no	Diffuse miliary tubercles.	Yes. Hilar nodes.
22. Strehl (40)	64	F	6.5	120%	12,000	1,000	yes	Numerous large and small foci with partial central caseation. One apple-sized wedge-shaped focus.	No TB in other organs.
23. Szczeklik (41)	39	F	7.8	76%	5,900	1,950	yes	Not stated.	Not autopsied. Pulmonary tuberculosis showed on roentgenograms.
24. Weil (43)	56	F	6.56	90%	48,000	1,350	no	Tubercles visible macroscopically.	Not stated.
25. Zadek (probable)(46)	31	F	6.62	110%	8,200		no	Unknown.	Probable.

* Gm.
† Mon ths

(28) case (No. 16) was an 11-month-old infant with ascites, purulent pleural effusions, purulent lymph node abscesses, splenomegaly, and a positive Mantoux text. Guinea pig inoculation of material from the pleural effusion and the abscess revealed tuberculosis. Forssell's (11) case (No. 8) had a polycythemia and roentgenographic evidence of calcium deposits in the spleen.

Polycythemia with pulmonary tuberculosis is rare. Holzberg (17) in 1929 reported the case of a 21-year-old male who had bilateral active pulmonary tuberculosis with sputum positive for tubercle bacilli and characteristic roentgenographic findings. In spite of repeated massive pulmonary hemorrhages, he maintained an erythrocyte count around 5.0 million with a hemoglobin of 90 to 105 per cent. Hayman (15) reported his analysis of tuberculosis in children with and without polycythemia and attempted to show that the polycythemia was not related to the splenic involvement, but rather to miliary tuberculous involvement of the lungs. If this were the case, however, polycythemia should be seen much more often than is the case in tuberculosis. There has, as yet, been no satisfactory explanation offered for the coexistence of these two conditions.

Many feel that the diagnosis of primary tuberculosis of the spleen is an indication for splenectomy. In Winternitz's (44) series of 51 patients, 17 had splenectomy performed and 59 per cent of these recovered. Of the 29 cases in which polycythemia and tuberculosis of the spleen coexisted, 7 had splenectomies. Of these, 4 patients died. In one (9), the erythrocyte count was still 8.8 million per cu. mm. on the ninth postoperative day, shortly before death. In another (40), the count after splenectomy went to 7.2 million with hemoglobin of 115 per cent, and 27,000 leukocytes per cu. mm. Of the 3 patients who recovered, there was no note of the blood count following surgery in one, but there was roentgenographic evidence that the miliary tuberculosis had cleared five years later. In the second, the initial count of 5.2 million went down after surgery, but gradually returned to the same count after four and one-half months. In the case of Bayer (2), the postoperative erythrocyte count was 6.0 million, but one month after surgery the count was 1.32 million per cu. mm. From these results it is difficult to evaluate the effect that splenectomy has on the polycythemia, the results being inconsistent and the series too small.

SUMMARY

1. A review of the literature disclosed 35 cases of tuberculosis of the spleen and polycythemia, to which another case is added.

2. Splenectomy is the treatment of choice if the diagnosis of primary tuberculosis of the spleen can be made. What effect this procedure will have on the coexisting polycythemia is problematical since the frequency of successful splenectomies in the past is too small for evaluation.

SUMARIO

Policitemia Secundaria a Tuberculosis Esplénica. Comunicación de un Caso y Repaso de la Literatura

1. Un repaso de la literatura reveló 35 casos de tuberculosis del bazo y policitemia, a los cuales se agrega otro caso.

2. La esplenectomía es el tratamiento de elección, si puede hacerse el diagnóstico de tuberculosis primaria del bazo. El efecto de este procedimiento sobre la policitemia coexistente resulta problemático por ser insuficiente para justipreciación el número de esplenectomías acompañadas de éxito en el pasado.

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EDITORIAL

Immunological Aspects of BCG Vaccination

There have been endless controversies concerning the dangers and effectiveness of immunization with the BCG vaccine. Surprisingly enough, however, little has been said or written concerning the immunological basis and the technical problems involved in the preparation of the vaccine or the measurement of its protective efficacy. Opponents as well as proponents of BCG vaccination seem to accept implicitly that the technical procedures advocated by Calmette and his associates for growing the microorganism, preparing suspensions of it, and assaying the development of immunity, are fundamentally adequate and need not be modified except in detail. This is a questionable assumption and there is much reason to suspect that many of the controversies elicited by BCG vaccination cannot be settled until a number of bacteriological and immunological problems have been solved. Indeed, it is not unlikely that many of the failures of vaccination can be traced to the utilization of defective vaccines and to the lack of techniques for differentiating between allergy and protective immunity.

The BCG vaccine is a suspension of living tubercle bacilli obtained from cultures of a strain so attentuated as to be incapable of causing progressive disease in experimental animals. It is almost certain that the immunity produced by the vaccine is the outcome of a limited but definite multiplication of the attenuated bacilli in the body of the animal undergoing immunization, chiefly in the regional lymph nodes. The degree of immunization probably reflects in a certain measure the extent of this multiplication. It is very likely, on the other hand, that the degree of multiplication depends in turn upon at least four independent factors: (a) the number of living microorganisms injected; (b) their physiological state; (c) their level of attenuation (or virulence); (d) the susceptibility of the immunized individual.

As far as can be judged from published experimental data and from present practice, these factors are not yet sufficiently understood to permit critical and quantitative assessment of the properties of the vaccine.

It is generally recognized that the numbers of viable bacilli in the BCG vaccines prepared by standard methods and kept in fluid medium decrease rapidly, even at ice box temperatures; considerable mortality of the bacilli also occurs at the time of desiccation when attempts are made to preserve the bacilli in the dried state. Although no adequate quantitative bacterial counts have been published, it is certain that the numbers of viable organisms injected as an immunizing dose under the conditions of present day practice vary many thousandfold, depending upon the origin of the vaccine, the time elapsed since its preparation, and the conditions under which it has been preserved. As measured by direct microscopic count or by dry weight of bacillary bodies, the vaccines currently distributed in this country and abroad contain from 1 to 5 billion bacterial cells per cc. of fluid. Viability tests reveal, however, that only a fraction of a per cent

of these cells, at times less than .001 per cent, are viable at the time of injection. In view of this fact, the general practice of giving directions in terms of cc. or mg. of vaccine is entirely meaningless and perhaps dangerously misleading since it tells nothing of the number of living bacilli per volume or unit weight.

The ability of all bacterial agents to multiply in the animal body, and the tubercle bacillus is no exception, depends not only upon the size of the viable infective dose but also upon the physiological state of the bacterial cells at the time of injection. The conventional techniques used in the cultivation and distribution of the BCG vaccine expose the bacilli to such a variety of chemical and physical trauma that any vaccine preparation consists of an unpredictable mixture of cells possessing all degrees of physiological age and activity. It is therefore imperative that techniques be worked out to obtain bacterial populations of a reasonable degree of homogeneity in order to control their ability to multiply *in vivo*.

It is obvious that, in addition to its physiological state, the intrinsic virulence of a culture is a determining factor of the extent to which it multiplies in susceptible animals. At least three general levels of intrinsic virulence have been recognized among mammalian tubercle bacilli. They are represented by:

(a) the classical virulent strains capable of causing progressive disease;
(b) the truly avirulent variants (illustrated by the various Ra cultures isolated at the Trudeau laboratory) which appear completely incapable of multiplying *in vivo*; and
(c) the "attenuated" strains which multiply to a certain extent *in vivo* but fail to cause progressive disease under normal conditions (such are the BCG strains and the culture RIRV isolated at the Trudeau laboratory).

As far as is known, all the strains of BCG presently in use are derived from the attenuated culture first obtained by Calmette and Guérin. Although there is as yet no incontroverted evidence that this culture has ever recovered full virulence, there is no doubt that it has undergone considerable variations in the course of its long career. And indeed, it would be very surprising if it had not. K. A. Jensen, for example, has pointed out that the strains available in Scandinavia at the end of World War II varied appreciably with reference to the severity of the skin lesions which they could elicit in normal guinea pigs. Similarly, it has been observed in our laboratory that three strains of BCG obtained from American collections differ significantly in their ability to produce pulmonary lesions in mice following intravenous injection. Here again, studies of the comparative virulence (or attenuation) of different strains will have quantitative meaning only when the inoculation dose is defined in terms more significant than the designation of the volume or weight of culture used.

It must be remembered also that any statement concerning the virulence of a culture should be qualified by specifying not only the species and the breed, but also the physiological state of the animal used for the test. Thus, it has been shown at the Saranac laboratory that the strain R1RV (in many respects difficult to differentiate from BCG) causes severe disease in the silicotic guinea pig but not in normal animals. It has also been found in our laboratory that one of the BCG strains commonly used for immunization can cause severe pulmonary

disease (and sometimes death) when injected in sufficient amounts into mice maintained on deficient diets. Presumably in most studies the physiologic state of the animals has not been altered in such a fashion. It is possible, however, that some of the conflicting reports concerning the virulence of BCG for guinea pigs might reflect the presence of differences in the physiologic state of the animals used by the various investigators.

Any immunization procedure must be standardized in terms of the specific goal for which it is employed. It is highly desirable, therefore, that BCG preparations be standardized in terms of their ability to induce immunity against tuberculous infection. Surprisingly enough, there is as yet no well defined technique for such an assay.

Most tests aimed at evaluating the immunizing efficacy of BCG have been carried out by injecting into guinea pigs or cattle amounts of vaccine far greater than those used in human vaccination. In some cases the amounts were so great (of the order of 10 mg. of bacillary bodies per Kg. of body weight) that a definite degree of immunity could have been achieved with the same weight of bacilli killed by heat. Needless to say, lmmunization tests carried out under such conditions do not reflect the immunizing efficacy of the vaccine as used for immunization of humans.

Of extreme importance also is the technique employed in the challenge infection used to assay the resistance of the immunized animal. When tubercle bacilli are injected intramuscularly or subcutaneously into immunized guinea pigs, they elicit the complex allergic reaction familiarly known as the Koch phenomenon. One of the results of the Koch phenomenon is that a large percentage of the bacilli are ejected from the tissues as soon as the lesion elicited by the allergic reaction begins to ulcerate. As this reaction does not take place in normal animals, it follows that the immunized guinea pig is subjected in fact to an infective dose of bacilli smaller than that which invades the tissues of the non-immunized controls.

For lack of quantitative information, it is not possible to evaluate the effect of this discharge or walling off of bacilli at the site of the ulcer on the greater resistance to artificial infection exhibited by vaccinated guinea pigs. It appears certain, however, that the importance of this effect is not small, as any decrease in the size of the infective dose markedly increases the survival time of the animals. Thus, in certain cases, the apparent immunity of guinea pigs following BCG vaccination might be nothing but a sort of immunological artifact resulting from the loss of a significant fraction of the inoculum.

It is possible that the shedding or walling off by the vaccinated guinea pigs of some of the bacilli injected intramuscularly or subcutaneously has its counterpart in human infection. But, even then, it is probable that many of the bacilli are distributed throughout the human tissues instead of being discharged outside the body. Thus, the Koch phenomenon, which probably results in some protection of the vaccinated guinea pigs against artificial infection, may fail to have a corresponding protective effect under the usual conditions of the human disease. Fortunately, there are many facts which suggest the existence of an

antituberculous immunity completely independent in its mechanism from tuberculin allergy. Much additional work is therefore required toward the formulation of techniques for evaluating the effectiveness of BCG as an immunizing agent under conditions that would reflect the processes at work in the human body.

In the final analysis the usefulness of BCG immunization must be measured by its ability to protect human beings and cattle against tuberculous infection. Field trials in cattle have been so unconvincing that the technique has never achieved widespread application in veterinary medicine. There are, however, a few studies on record which appear to prove that, in selected situations and when the immunization tests are carried out with sufficient care, it is possible to achieve with BCG vaccination a significant degree of immunity in human populations. There are also, on the other hand, many records of failure. It has been argued that these failures were due to faulty immunization procedures but there is no way to prove or disprove this contention because there is no method, short of infection, to measure protective immunity.

The development of a positive tuberculin test is universally used as a criterion that the vaccine has "taken" but, unfortunately, as already pointed out, the relation of tuberculin allergy to immunity is one of the most obscure aspects of the pathogenesis of tuberculosis. It is possible to render animals tuberculin positive by injecting dead tubercle bacilli into them without increasing thereby their resistance to infection. It is well possible that under certain conditions injection of BCG may also bring about a state of allergy without inducing immunity. So important is the necessity to differentiate between allergy and immunity that it may be useful to illustrate the difference by examples taken from two other bacterial infections.

The use by Pasteur of living attenuated cultures for immunization against anthrax (the first forerunner of BCG immunization) resulted in spectacular protection of animals provided the challenge infective dose was given within a fairly short period of time after vaccination. Pasteur himself, however, soon recognized that the immunity was only transient and he advised that the vaccination be repeated every year, preferably just before the beginning of the anthrax season. Nevertheless, it is now known that long after vaccination has lost its protective effect against infection there are still present in the vaccinated animal antibodies, some of which are capable of giving rise to allergic reactions, which bear no relation whatever to immunity. To look for these anthrax antibodies would give no information as to the resistance of the animal to anthrax infection.

The extensive knowledge of the immunochemical reactions involved in streptococcal diseases affords also a striking example of dissociation between immunity and allergy. Infections caused by human streptococci of group A bring about a state of tuberculin-like allergy to the streptococcal "nucleoprotein" fraction. It has been demonstrated beyond doubt that, far from resulting in any increased resistance to streptococcus disease, this allergy may be the cause of severe pathologic lesions. On the other hand, a highly effective and type-specific resistance

to infection is elicited by an antibody specifically directed against an entirely different streptococcal protein, the so-called M substance. It has been thoroughly established that the state of allergy to the "nucleoprotein" and the immune resistance due to the M antibody are completely independent one from the other. Following natural infection or immunization, both allergy and resistance may coexist or only one may be present, depending upon certain immunological conditions that need not be discussed here. Thus, a test devised to measure streptococcal allergy does not measure resistance to streptococcus infection and, by analogy, the tuberculin test does not necessarily reflect immunity to tuberculosis.

It must not be forgotten, moreover, that the response of an individual to an immunizing procedure is greatly affected by his physiological state. It is even conceivable that many of the classes of human beings who are most dangerously exposed to tuberculosis (for example those living under conditions of great economic stress, with inadequate food supplies) may be those least capable of responding satisfactorily to immunization procedures. For all these reasons, it is urgent that techniques be developed for the measurement of true immunity (not tuberculin allergy) in order that the BCG immunization programs can be intelligently controlled.

Unfortunately, we are still in complete ignorance of the immunological mechanisms, humoral or cellular, which bring about immunity to tuberculosis. It is not yet possible, therefore, to devise any laboratory test that would control the effectiveness of BCG vaccination. Nevertheless, BCG is the only immunizing agent for which there is enough experience to warrant administration to human beings, and the urgency of the practical problems of tuberculosis may compel its use even though so much is ignored of its immunological properties.

The advisability of undertaking a BCG immunization program in any given community has to be decided on the basis of many clinical, epidemiological, and social factors which do not come within the province of the present discussion. But what we have tried to emphasize is that BCG immunization, like any other public health measure, must satisfy a number of minimal requirements of dependability, predictability, and evaluation of efficacy. It is because these requirements were ignored that most of the vaccines and sera introduced into medical practice in the past have now been completely discredited. It is to be feared that the same fate will happen to BCG, unless steps are taken soon to learn to control the factors which determine the efficacy of immunological procedures, namely: the effective size of the immunizing dose, the antigenic potency of the vaccine, and the response of the immunized individual in terms of protective immunity. The analysis of these factors and the development of techniques by which they can be quantitatively evaluated come within the range of the classical approach to bacteriological and immunological problems and would seem to be the responsibility of those who advocate the widespread use of BCG as an immunizing agent.

René J. Dubos

BOOKS

GERHARD HERTZBERG: *The Achievements of BCG Vaccination. Pp. 270. I. Johan Grundt Tanum Forlag, Oslo, Norway, 1948.*

In spite of the fact that BCG is being widely used throughout the world at the present time in an attempt to immunize against tuberculosis, the subject of its use is still highly controversial.

It is generally agreed that a great deal is still to be learned concerning the degree of immunity the vaccination confers, the stabilization of its potency, the optimum method of use, the optimum dosage, the duration of the immunity conferred, and adequate means of testing the duration of immunity.

Studies which will add to our information on any of these or related subjects concerning BCG are being awaited with the greatest interest.

In *Achievements of BCG Vaccination* by Gerhardt Hertzberg, a great mass of valuable information is collected and illustrated by material from the Tuberculosis Department of the Oslo Public Health Service.

Investigations on the influence of sex, age, and dose, as well as studies on the virulence of BCG and on the size of the local reaction, are presented with statistical analyses. Other studies presented include those on the size of the local reaction and its relation to the development of tuberculin sensitivity; the duration of the tuberculin allergy following vaccination, the possibility of ill effects following vaccination; and the results of various investigations throughout the world on tuberculosis morbidity and mortality following vaccination with BCG, with special reference to the results obtained by the Tuberculosis Department of the Oslo Public Health Service.

The difficulties of conducting a BCG program on a public health basis, where vaccination and follow-up are entirely on a voluntary basis are clearly presented. As an example, it was hoped that all BCG-vaccinated persons could be tuberculin tested and examined roentgenographically one year after vaccination but, in spite of all attempts to return them to the clinics, there remained an extremely high percentage of absentees. With our present indefinite knowledge of BCG activity, the tuberculin test at the end of the year seems most necessary for, if the test has reverted to negative, revaccination is advised.

A section of the book is devoted to information obtained on the duration of tuberculin sensitivity following the BCG inoculation by various methods employed. The results of these studies are of great interest, for they show that the duration of the vaccination allergy is not a constant factor but is influenced by the degree of tuberculin sensitivity following BCG vaccination. Regardless of method of vaccination, the greater the tuberculin sensitivity following vaccination, the longer the duration of tuberculin allergy.

A further finding was that the duration of tuberculin allergy was longer following intracutaneous inoculation than when the multiple puncture method of Rosenthal was used.

Among the interesting sections in the book is one dealing with the virulence

of the vaccine. It is pointed out that "Calmette's original claim that he had succeeded in converting the BCG strains into a virus fixe is no longer upheld by authorities on BCG." Evidence is presented showing that the virulence of the vaccine may decline to such a degree that it provokes no tuberculin reaction. On the other hand, Jensen is quoted as stating that "if the strain becomes too virulent, abscesses develop with alarming effect." According to Jensen, the most sensitive criteria known for determining the virulence of a given vaccine are the size of the local reaction, the frequency of development of tuberculin sensitivity after vaccination, and the degree of tuberculin sensitivity on re-examination two months after vaccination.

However, in spite of the fact that at times a certain increase in virulence of the vaccine occurs it must be added that there is no evidence that it has at any time created any greater hazard than the production of local lesion abscesses. As a matter of fact, the more frequent difficulty has been a diminution in the virulence of the vaccine. This problem, which has been discussed in the United States, is of practical importance. The vaccine, as used, is an emulsion of BCG in suspension in which there may be great variations per unit of volume in the total number and in the relative numbers of living, damaged, and dead BCG organisms. It is difficult, therefore, to have full dependence on a vaccine suspension where the potency is much higher on the second or third days than on the eighth or ninth days after preparation.

The material presented seems to give no support for the assumptions that BCG vaccination is harmful in the pre-allergic stage or that natural tuberculosis infection in the incubation period of BCG vaccination is dangerous. However, it is emphasized that, as far as can be ascertained, BCG vaccination does not afford any protection against tuberculosis when natural infection occurs before complete vaccination allergy has been achieved.

In any publication of the subject of BCG the greatest interest lies in the section dealing with the efficacy of the vaccine in the prophylaxis against tuberculosis.

Before presenting the results of their own investigations, a summary is made of certain other studies reported from various countries. These are the same studies which have so often been presented and criticized in discussions on the efficacy of BCG.

In some studies the value of the vaccine is claimed on basis of a reduction in tuberculosis morbidity in the vaccinated cases. But since the BCG inoculation is the primary tuberculosis focus, one should not expect the benign exudative pulmonary process in exposed vaccinated cases while expecting a certain number among the controls.

Studies are presented entirely lacking in controls. Among these is the study of Wallgren in Gothenberg "where practically no control material was available." In this city where, with very few exceptions, all infants exposed to tuberculosis were vaccinated with BCG, the fall in tuberculosis mortality dropped in a six-year period from 400 to 30 per 100,000 for infants, whereas the general tubercu-

losis mortality dropped from 200 to only 100 per 100,000 in the same period of time.

These figures appear of great significance by themselves but when a comparison is made with the figures from New York City, where BCG was not used, the importance becomes less pronounced.

In New York City with a population that includes over 600,000 Negroes, the tuberculosis mortality in children under the age of 15 years has dropped 94% since 1915. In that year the tuberculosis mortality was 81 per 100,000, whereas in 1947 it was only 5 per 100,000, a significant reduction.

The carefully controlled studies on BCG in New York City, where very little difference in the tuberculosis mortality was found between vaccinated and control cases, are criticized on the ground that the children were in many instances permitted to return to a tuberculous environment immediately after vaccination.

On the other hand, the favorable studies of Aronson are praised although his cases were not selected by alternation, as had been carried out in New York City, and in spite of the fact that no separation was attempted or carried out.

Among the studies presented in the book is one that deserves special attention. This is a report by Hyge of 200 girls between the ages of 12 and 18 years who were exposed to a tuberculous teacher in a school in Denmark. One hundred and six of the girls had received BCG whereas 94 were tuberculin-negative but had not been vaccinated.

Of the 106 girls who were vaccinated with BCG and who were exposed, 2 developed pulmonary tuberculosis within three years requiring pneumothorax treatment. On the other hand, of the 94 girls not vaccinated, 79 became tuberculin-sensitive, among whom 41 developed pulmonary tuberculosis (37 with tubercle bacilli found on gastric lavage). After three years, one had died of tuberculosis and 5 were undergoing pneumothorax.

This report would seem to give support to the impression that the pulmonary infiltration of primary tuberculosis is much more likely to become progressive and advance to caseation in the adolescent than in the young child. If this is true, then vaccination with BCG, which places the primary focus at the point of inoculation, would be most valuable since it is extrapulmonary.

Of greatest interest to the reader is the report of the studies conducted in Oslo by the Public Health Service under the supervision of the author himself, Doctor Hertzberg. What scientific standards of investigation were laid down and what efforts were made to obtain adequate controls, controls which could be truly comparable to the individual vaccinated?

On page 30 one comes across an amazing statement, "The main qualifications for inclusion in the control material is the evidence (in our records) of recent infection with tuberculosis in persons who had earlier been tuberculin negative."

In other words, every individual vaccinated with BCG gave no evidence of having been infected with tubercle bacilli, while every control was already infected with tubercle bacilli. "No one is vaccinated with BCG unless he is Mantoux-negative to 1.0 mg. of Old Tuberculin."

Such experimental methods immediately destroy any value to be obtained from a study of tuberculous mortality statistics.

Needless to say the tuberculosis mortality in the control groups is very much greater than that of the vaccinated group, a ratio of 45 to one.

It is indeed unfortunate that in this volume prepared under the supervision of statisticians one can gain no further information as to the efficacy of BCG.

However, there is a great deal to be found concerning the side effects of BCG, such as local reaction and its relation to duration of tuberculin sensitivity, discussions concerning the potency and virulence of the vaccine, and studies on superinfection after loss of vaccination allergy. An excellent bibliography is also included.

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CARL MALMBERG: *140 Million Patients. Pp. xii + 242. Reynal & Hitchcock, New York, 1947. Paper. Price $2.75.*

This book emphasizes some defects in American medicine today. Its subtitle, *The Revealing Facts Behind Health and Medical Care in America*, is misleading, and might better read *Some Revealing Facts Behind Health and Medical Care in America*, for the author deals in considerable detail with many medical defects, whereas he passes over the excellencies of American medicine in glittering generalities. However, his data are worthy of consideration, for he brings out many points all too often ignored by medical men.

The author, we are told, has been a public relations advisor, information specialist for the United States Public Health Service, and Chief Investigator for the United States Senate Subcommittee on Health and Education.

In his first chapter, *Health Inventory—U. S. A.*, he attacks the often heard idea that the United States is the healthiest country in the world by quoting what would seem to be reasonably valid statistics compiled by the Department of Commerce, Bureau of the Census. He shows that in 1938, considered the last normal pre-war year, 7 countries showed a lower *crude* infant mortality rate in those under one year old per thousand live births, Iceland showing the lowest. As to maternal mortality per thousand live births, 21 countries showed lower crude rates, Japan having the lowest. What *corrected* rates would show, we do not know. While the tuberculosis death rate between 1920 and 1936 decreased in the United States 51.2 per cent, five countries showed an even greater percentage decrease, the Netherlands leading with a decrease of 66.0 per cent.

In *The Cost of Sickness*, expensive proprietary drugs as well as patent medicines are properly scored. Rebates to physicians on high charges for the rental of oxygen equipment to patients and on prescriptions for eyeglasses are justly condemned. The economic waste of competing costly equipment owned by individuals is discussed. Blatant quackery and voodooism are mentioned.

How Good is American Medical Care? lists many examples of medical incompetence and inefficiency, both individual and institutional. The inequality of dis-

tribution of medical care is also discussed. Unnecessary operations are properly castigated. Even the free clinics of Washington, D. C. are a target for the author. A quotation said to be verbatim from certain testimony before the Senate Committee on Education and Labor, if correct and not torn from its context so as to distort its meaning, seems worth quoting in part:

Senator Pepper: "Do you think the American people have all been well?"
Dr. S.: "Yes, I know that they have."

State service for crippled children is deservedly praised.

Mr. Malmberg favors President Truman's fivefold program, which includes:

1. federal financial aid to build hospitals, health centers, et cetera;
2. federal aid in expanding public health and maternal and child health services;
3. federal aid to train doctors and health workers and for medical research;
4. incorporation of health insurance in our social security system;
5. cash insurance protection against loss of earnings from sickness or disability.

Mr. Malmberg, admitting that item 4 is the most controversial one, believes that item 1 depends on it, for it would be of little use to build hospitals that people could not afford to use.

Voluntary Plans, Too Little and Too Late attacks the ultraconservatism of the A.M.A., which seems at times to have followed, rather than led, the movement for better medical service to the underprivileged and isolated. Often Negroes are excluded from voluntary insurance plans.

The final chapter, *140 Million Patients Can't Be Wrong*, expresses the idea that the people of the United States, *i.e.*, the potential patients, will determine the type of the medical practice of the future. The chapter title is a half-truth, for a large number of the 140 million patients consume an incredible amount of useless or worse patent medicine, as Mr. Malmberg admits. We wonder if the volume of work, expressed in financial terms or in the number of patients, of the best clinics in the country can equal that of the most notorious patent medicine businesses. The latter gives evidence that a vast number of the 140 million patients *can* be wrong.

The book is an able argument for socialized medicine, but ignores the arguments against it, such as the destruction of the will to get well, et cetera. Space forbids the presentation of the other side. With about 180,000 doctors in the United States and with human nature as fallible as it is, there must be numerous cases of incompetence or neglect under any system of practice, individual or socialized. Very few physicians want completely socialized medicine. None want to assume individual care of all the insane. Most of us want a great increase in both the quality and quantity of the care of mental patients by the state and of many other chronic cripples unable to care for themselves. However, whatever our views on the degree of socialization of medicine that is desirable, we would be worse than foolish to deny the existence of defects in our present day methods. We must face them and constantly strive to eradicate them and build constructively for a better future.

If Mr. Malmberg proves to be a Socratic gadfly that stings us into a realization of our deficiencies, he will perform a useful task. The combined sincere thought of conscientious, balanced, enlightened people, in and out of the medical profession, may serve as a Socratic midwife to determine which of the author's ideas are true births and which are expulsions of wind. We do not think that any enlightened person can condemn the book as all wind. Rather we believe that it contains much truth, some error, and *it certainly fails to present the essential weaknesses in socialized medicine.* It is a good antidote for ultraconservatism in medicine, but might well be published in a single volume along with as frank a discussion of the evils of socialized medicine as the author gives of the evils of a system based on rugged individualism or a too slavish adherence to tradition.

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AMERICAN TRUDEAU SOCIETY

Medical Section of the National Tuberculosis Association

STATEMENT ON BCG

(Revised statement submitted to the ATS Committee on Medical Research and Therapy in Detroit, April 30, 1949, by Dr. E. P. K. Fenger, Oak Terrace, Minnesota, chairman of the Subcommittee on Immunology, and subsequently submitted to the ATS Council at its meeting in Detroit on May 1, 1949, through Dr. H. McLeod Riggins, chairman of the Committee on Medical Research and Therapy. The statement as revised was adopted by the Council.)

The members of the Society and other physicians in the United States have been interested for many years in the active immunization against tuberculosis with BCG. The expansion of public health activities in the field of tuberculosis control by official and voluntary agencies and the acquisition of new knowledge concerning immunity in tuberculosis have prompted the American Trudeau Society to make the following observations and recommendations:

I. BCG vaccine prepared under acceptable conditions, and administered by approved techniques to persons negative to tuberculin, can be considered harmless.

II. The degree of protection recorded following vaccination is by no means complete, nor is the duration of induced relative immunity permanent or predictable. The need for further basic research on the problem of artificial immunization against tuberculosis is recognized and is to be emphasized. Studies should be directed toward:
   (a) improvement of the immunizing agent;
   (b) development of criteria for vaccination and revaccination;
   (c) more accurate determination of which groups in the general population should be vaccinated; several well controlled studies are underway at the present time;
   (d) promotion of carefully controlled investigative programs, which, as a rule, will be carried out best under the auspices of official agencies such as the Public Health Service, state and municipal health departments, and other especially qualified groups;
   (e) devising of adequate record systems for management of statistical problems involved in recording and following large numbers of vaccinated people.

III. On the basis of studies reported in the literature, an appreciable reduction in the incidence of clinical tuberculosis may be anticipated when certain groups of people who are likely to develop tuberculosis because of unusual exposure, inferior resistance, or both, are vaccinated.
   (a) In the light of present knowledge, vaccination of the following more vulnerable groups is recommended, provided they do not react to adequate tuberculin tests:
      1. doctors, medical students, and nurses who are exposed to tuberculosis;
      2. all hospital and laboratory personnel whose work exposes them to contact with the bacillus of tuberculosis;
      3. individuals who are unavoidably exposed to infectious tuberculosis in the home;

4. patients and employees in mental hospitals, prisons, and other custodial institutions in whom the incidence of tuberculosis is known to be high;
5. children and certain adults considered to have inferior resistance and living in communities in which the tuberculosis mortality rate is unusually high.

IV. It is recommended that efforts be continued to perfect and to meet in practice suitable standards for the production of BCG vaccine and that, when practicable, commercial firms be licensed under the National Institutes of Health to produce this vaccine.

V. The Society believes that, since BCG vaccination affords only incomplete rather than absolute protection, the most effective methods of controlling tuberculosis in the general population are:
(a) further improvement of living conditions and the general health;
(b) reduction of tuberculous infection, which can be accomplished by modern public health methods and the unremitting search among presumably healthy individuals for patients with infectious tuberculosis;
(c) prompt and adequate medical and surgical treatment of patients with active disease;
(d) segregation and custodial care of those not amenable to accepted forms of therapy;
(e) adequate rehabilitation.

VI. It is to be emphasized that BCG vaccination must not be regarded as a substitute for approved hygienic measures or for public health practices designed to prevent or minimize tuberculous infection and disease. Vaccination should be regarded as only one of many procedures to be used in tuberculosis control.

VII. Expansion of modern diagnostic, therapeutic, and rehabilitation facilities is required at this time to make full use of these new methods which can accomplish further dramatic reduction of tuberculosis mortality and morbidity rates in the United States.

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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CLINICAL STUDIES, TUBERCULOSIS

Avian Tuberculosis.—Up to 1938, there were 13 proved cases of avian tuberculosis in man; 24 others were reported but in them the proof is regarded as insufficient. Adequate proof consists of thorough pathogenicity tests using hens, rabbits, and guinea pigs. In Denmark since 1935, avian tubercle bacilli giving characteristic pathogenicity reactions have been cultured from 6 human cases. Four of the patients had lymphadenitis and one each had pulmonary and meningeal tuberculosis. In 2 cases, cutaneous tests made with avian tuberculin yielded positive results to 0.00002 mg.—*Avian tuberculosis in man, I. Gragsted, Lancet, July 16, 1949, 1: 123.*—(*A. G. Cohen*)

Congenital Tuberculosis.—In congenital tuberculosis the infection reaches the fetus either via the umbilical vein or from infected amniotic fluid. The second mode of infection occurs through ingestion of such fluid by the fetus, in which case the primary seat of the disease is the intestinal tract with resultant enlargement of the mesenteric and porta hepatis glands. Some investigators have maintained that an infection from amniotic fluid may be caused by aspiration; this view is doubted by others, there being no definite proof that amniotic fluid enters the lungs. A case of proved congenital tuberculosis occurred in an infant who appeared normal at birth and weighed 8 pounds. The mother was a 31-year-old woman with bilateral pulmonary tuberculosis. On the twenty-second day after birth the child began to take his feedings poorly; he died on the thirtieth day. Autopsy revealed a generalized, disseminated tuberculosis, principally of the glands in the hilum of the liver. The mother died three weeks post partum. Autopsy demonstrated a disseminated tuberculosis particularly of the peritoneum, ovarian tubes, and lungs. It is believed that the infant had a congenital tuberculous infection because: (*1*) the child's extrauterine life was similar to others reported; (*2*) his tuberculous lesions were commensurate in size and distribution with those following intrauterine infection; (*3*) the mother had active genital tuberculosis; (*4*) the child was immediately removed from contact with the mother and there was found no subsequent source of tuberculous infection among the attending staff.—*A case of congenital tuberculosis. J. W. Jordan & H. Spencer, Brit. M. J., February 5, 1949, No. 4596: 217.*—(*R. W. Clarke*)

Lupus and Bone Tuberculosis.—Thirty-three patients with lupus were subjected to routine roentgenographic examination of the entire skeletal system. Of these patients, 8 had active bone tuberculosis; 8 others were known to have had bone tuberculosis in the past but it had healed. In addition to these known lesions, roentgenograms revealed latent osseous foci in 20 cases (60.6 per cent). A total of 46 unsuspected bony lesions were discovered. The involvement usually appeared as a circumscribed round or oval area of consolidation in the bony substance; the sizes most frequently encountered were 3 by 5 mm. and 4 by 6 mm. These lesions are considered to be of tuberculous etiology.—*Latent bone involvement in patients with lupus (a preliminary report) (Russian), I. N. Grinchar, Probl. tuberk., November-December 1948: 32.*—(*V. Leites*)

Coccidioidomycosis and Tuberculosis.—A 21-year-old Japanese-American, who had lived five months in San Joaquin Valley, developed malaise, asthenia, nonproductive cough, a vesicular eruption of the fingers, and acute pleurisy on the left with an effusion. Coccidioidin and tuberculin skin tests were positive. Ten months later an abscess appeared over the sternum. A few months later the following symptoms and signs developed: anorexia, weight loss, headaches, palpable nodules on the scalp, pain and swelling over the dorsum of the left foot, and fever. Acid-fast bacilli were found in the gastric contents. Pus aspirated from the abscess of the foot contained *Coccidioides immitis*. A chest roentgenogram revealed nodular infiltrations in both lungs. Before he died the patient developed multiple abscesses; the pus contained *Coccidioides immitis*. The pathological diagnoses were: (*1*) coccidioidomycosis of the lungs, peritoneum, left shoulder joint, left ankle, skull, and dura; and (*2*) tuberculosis of the lungs, hilar lymph nodes, liver, spleen, kidneys, peritoneum, adrenal glands, prostate seminal vesicles, sternum, pericardium, and ileum. This is the first case report of coexisting disseminated coccidioidomycosis and disseminated lymphohematogenous miliary tuberculosis.—*Disseminated coccidioidomycosis and lymphohematogenous tuberculosis: Report of a case, B. Hyde & L. Hyde, Arch. Int. Med., 1949, 83: 505.*—(*G. C. Leiner*)

Calciferol for Skin Tuberculosis.—Charpy's regimen of massive oral doses of calciferol has been modified somewhat by the author. The latter recommends more intensive therapy during the first five weeks of treatment, using calciferol 15 mg. three times during each of the first two weeks, twice during each of the next three weeks and once weekly thereafter. A salt-free diet is employed on each treatment day and ascorbic acid 500 mg. are given daily during the first two weeks. Calciferol therapy is contraindicated in active pulmonary tuberculosis, renovascular disease, hypercalcemia, and senility. The treatment probably increases the defensive ability of the skin in some unexplained manner.—*Few notes on a modern method of treating cutaneous tuberculosis (Czech), J. Horachek, Lekarske listy, May 15, 1948, 3:* 269.—(*J. Ilavsky*)

Rib Fracture from Coughing.—Fractures of the ribs resulting from coughing often are recognized but probably are more frequent than the reports indicate. Seven new cases are reported. The mechanism by which the fractures are produced is difficult to determine. Primary tuberculous osteitis is generally believed to be so uncommon that it is unlikely to be the basic case. A cold abscess arising from an adjacent, caseous gland is a possible explanation. Fractures during coughing have occurred in healthy subjects, possibly associated with an increased fragility of the bones. The apparent high incidence in tuberculous patients suggests an effect of the infection on bony structures but the repeated chest roentgenogram makes it more likely that the lesion will be discovered in these persons. There is no evidence that tuberculous patients are particularly liable to decalcification except in so far as prolonged bed rest may lead to demineralization. The blood calcium concentration is normal in tuberculous patients and fractures heal normally without delay in calcus formation. Fractures from coughing seem to occur because the violent, abnormal action, probably associated with asymmetrical posture, produces an uneven tension on the ribs.—*Cough fracture of ribs, R. C. Cohen, Brit. M. J., January 22, 1949, 4594: 133.*—(*R. W. Clarke*)

Cavernostomy.—Of 75 cavernostomies, 67 were performed for cavities persisting after thoracoplasty, 3 for cavities which perforated through the chest wall during thoracoplasty, and 5 for cavities whose closure by thoracoplasty was not attempted. There were 11 deaths (16 per cent), 4 of which occurred in the immediate postoperative period. In this series, 83.5 per cent of the patients were considered "cured" or greatly improved. Contralateral pneumothorax was employed with 9 patients and contralateral thoracoplasty with

one. Most of the patients were in poor general condition at the time of operation; 35 subsequently were well and showed complete local healing. In 2 of the latter, new cavities appeared and necessitated further rib resections; in 2 others, new cavities were treated with a second cavernostomy. Six patients improved greatly and their sputum became negative for acid-fast bacilli although epithelization of the residual opening was slow. Nine other patients were greatly improved but had only a short follow-up period. The cavity was always localized by tomographic studies and was approached by the axillary route if possible. Parenteral and local streptomycin seemed to improve the results. The postoperative care was often very prolonged and most of the unsatisfactory results were attributed to the patients' leaving the hospital too early. The authors feel that the superiority of their results to those of American surgeons is due mainly to the greater emphasis in France on prolonged and meticulous postoperative care following cavernostomy. The procedure is especially indicated in all patients with low respiratory function of the contralateral lung. —*Resultats de speleotomie et quelques precisions de technique, A. Bernou, L. Goyer, Mareceaux & J. Tricoire, Rev. de la tuber., 1949, 13: 280.*—(*V. Leites*)

Clinical Studies, Nontuberculous Diseases

Bauxite-fume Pneumoconiosis.—A fatal pulmonary disease attributable to fumes containing bauxite recently has been discovered, chiefly among furnace feeders and crane operators. These men are exposed to dense white fumes during the fusion of finely ground Arkansas bauxite, iron, and coke to produce "corundum," an aluminum-oxide abrasive. Clinically the disease is characterized by shortness of breath, cyanosis, substernal discomfort, and recurrent episodes of spontaneous pneumothorax from emphysematous bullae. Examination of the chest reveals signs consistent with the parenchymal changes and often with pneumothorax. Roentgenographic changes are distinctive and quite different from those seen in other pneumoconioses. The cardinal features are diffuse, irregular, lace-like and granular shadows, greatly increased width of the mediastinum and collapse of the lung. In 6 fatal cases the specific pathological findings were confined to the lungs. Grossly there was diffuse, widespread induration without nodulation; large, emphysematous vesicles were frequent, often reaching a giant size. The hilar nodes were neither enlarged nor hard and were completely free of nodulation. Microscopically the lungs always showed diffuse fibrosis, the result of hyalinization of the alveolar walls; doubly refractile particles frequently were demonstrated by polarization microscopy. The causative fumes consist principally of amorphous material in particles not greater than 0.5 μ in diameter. These fumes have an average silica content of 36 per cent and alumina content of 50 per cent. The ashed residue of lungs from fatal cases contained 27 per cent silica and 33 per cent alumina. This affords some evidence that the amorphous alumina dust is the dominant etiological agent since no human disease has yet been ascribed to silica particles as small as those in the fumes. It is still undetermined whether silica plays an active but adjunctive role in the production of this disease.—*The morphology of bauxite-fume pneumoconiosis, J. P. Wyatt & A. C. R. Riddell, Am. J. Path., May, 1949, 25: 447.*—(*J. S. Woolley*)

Circumscribed Bronchitis.—Circumscribed bronchitis as a clinical entity was recognized in the course of bronchoscopic examinations. It usually involves the stem bronchi and the first few centimeters of the lobar bronchi, especially those of the lower lobes, being chiefly unilateral. The findings are those of mucosal inflammation of varying degree, the main feature of which is its circumscribed character. Swelling of the mucosa was frequent and was present in 50 per cent of the cases. Redness, hypersecretion, and increased sensitivity to cough-producing stimuli also were found. The diagnosis was made because

the symptoms suggested more serious involvement so that bronchoscopy was performed. In the 50 cases diagnosed as circumscribed bronchitis, bronchoscopy was done for the following reasons: hemoptyis (22 cases); persistent cough (6 cases); marked dyspnea (8 cases); abnormal expectorations (14 cases). In some cases, tissue was removed and showed only simple inflammatory changes. A few bronchoscopic applications of adrenalin to the involved area produced a rapid improvement or cure. The development of an increased cough reflex in a circumscribed part of the bronchial mucosa is believed to be the basis of the condition but the etiology is admittedly obscure.—*La clinique des bronchites circonscrites, J. M. Lemoine & J. de Léobardy, Presse méd., May 7, 1949: 404.*—(*V. Leites*)

Toxic Effects of Pontocaine.—Amethocaine hydrochloride (Pontocaine) can produce severe toxic reactions; 12 deaths have been reported following its use before bronchoscopy and gastroscopy. Such deaths are the result either of sensitivity or of overdosage and present the classic picture of cocaine poisoning. Amethocaine is ten times more potent than procaine or cocaine, is quick acting, and has a prolonged effect. It also is more toxic than cocaine. Amethocaine penetrates the tissues more rapidly than cocaine and does not produce vasoconstriction so that adrenalin must be used with it. The following prophylactic measures are suggested: premedication with barbiturates; administration of an amethocaine pastille thirty minutes before the examination; addition of adrenalin 1:1,000 solution in the proportion of 4 to 1 by volume; limitation of the total dose of amethocaine to 4 cc. of a 2 per cent solution; avoidance of the use of the laryngeal spray. The drug should not be applied to an inflamed, traumatized, or highly vascular surface. To control a toxic reaction, an unobstructed airway must be secured by an endotracheal tube if necessary; artificial respiration should be given with an oxygen-carbon-dioxide mixture; a rapidly acting barbiturate may be injected intravenously and respiratory and cardiac stimulants administered.—*Amethocaine hydrochloride: Severe toxic effects when used for bronchoscopy, C. A. Jackson, Brit. M. J., January 15, 1949, No. 4593: 99.*—(*R. W. Clarke*)

Spontaneous Rib Fracture.—A 68-year-old white man with bronchial asthma, severe cough, dyspnea, and pain in the right chest was found to have spontaneous fractures of the eighth, ninth, and tenth ribs on the right side. Another roentgenogram taken several months later showed callous formation over these fractured ribs. It was felt that the opposing action of two sets of muscles is necessary to produce this type of fracture. A contraction of the serratus anterior, which exerts a pull laterally and cephalad as opposed to the simultaneous pull of the external abdominal oblique medially and caudad, is the most likely cause. Spontaneous rib fracture occurs only rarely in bronchial asthma.—*Spontaneous rib fracture in bronchial asthma, M. L. Gelfand, Ann. Allergy, March-April, 1949, 7: 217.*—(*L. Hyde*)

Rib Fracture from Coughing during Pregnancy.—Rib fracture due to coughing occurred during late pregnancy in 4 women, none of whom was known to have fragile bones. Slight osteoporosis was found in only one patient; all 4 had blood calcium and phosphorus concentrations within normal limits. Such fractures usually produce a severe, sharp pain during a fit of coughing. The sensation often is described as that of something "giving" or "cracking" in the chest. A mild fever may follow and a pleural rub occasionally is noted. A localized area of tenderness is present on one or more ribs. The ninth, tenth, and eleventh ribs are the most likely sites of the fractures and they are more frequent on the left side. The mid-thoracic fractures occur along the interdigitation of the external oblique and anterior serratus muscles and are assumed to be the result of shearing stress. The likelihood of fracture is reported to be increased if the serratus is taut at the time of coughing as it may be when the arm is raised or when the

patient is resting on one elbow. From this study it seems likely that fractures of the lower ribs are caused by the shearing stress of the external oblique and the costal slips of the latissimus dorsi. The posture of late pregnancy also may play a part. Another possible cause is the driving of the uterine mass backwards and upwards against the inner surface of the lower chest by contraction of the anterior abdominal muscles in coughing. This force would be deflected to the left by the liver. Although a fractured rib is a trivial injury, it can produce extreme discomfort and insomnia. The importance of recognizing the fracture lies in the great relief afforded by early and adequate strapping of the chest. Equally important is the avoidance of tiresome confinement to bed and needless investigation, often in a hospital.—*Cough fracture in late pregnancy, J. W. Paulley, D. H. Lees, & A. C. Pearson, Brit. M. J., January 22, 1949, No. 4594: 135.*—(*R. W. Clarke*)

Spontaneous Mediastinal Emphysema.—Two cases of spontaneous pneumomediastinum developed during labor associated with severe straining. The clinical course in each case was uneventful with recovery in a few days. In differentiating the condition from pneumopericardium, the important points are the presence of air in the neck, the milder symptoms and, in the roentgenogram, the air along the left cardiac border extends above the level of the pericardial sac.—*Spontaneous pneumomediastinum in pregnancy, D. J. MacRae, Lancet, May 21, 1949, 1: 902.*—(*A. G. Cohen*)

Spontaneous Mediastinal Emphysema.—A woman in her eighth month of pregnancy developed spontaneous mediastinal emphysema during an asthmatic attack. The diagnosis is simple if subcutaneous emphysema appears. Otherwise, two important diagnostic features are: (*1*) an auscultatory crunch during cardiac systole (Hamman's sign), and (*2*) the presence in roentgenograms of radiopaque lines running parallel to the vetebral column in line with the tips of the transverse processes and of a narrow area of translucency between them and the root shadow, representing air pockets lining the lateral boundaries of the mediastinum.—*Acute mediastinal and subcutaneous emphysema, L. Fridjohn & P. G. Azzopardi, Lancet, May 24, 1949, 1: 904.*—(*A. G. Cohen*)

Bronchogenic Carcinoma.—Phalangeal metases from any carcinoma are rare. Three cases of metastases to the phalanges from bronchogenic carcinoma are reported. In all 3, the lesions at first seemed to be inflammatory but roentgenograms showed bone destruction. Aspiration biopsy was diagnostic in 2 of the cases.—*Phalangeal metastases in bronchogenic carcinoma, G. M. Colson & A. Willcox, Lancet, January 17, 1948, 1: 100.*—(*A. G. Cohen*)

Surgical Treatment of Bronchiectasis.—Since the introduction of aerosol penicillin, the patients come to the operating room with "dry lungs." Bronchoscopy is not done in the immediate preoperative period; it results in the patients becoming poor anesthetic subjects. Simple anesthetic procedures are practised. A small amount of sedative medication is given two hours before operation. Anesthesia is induced with intravenous pentothal. A mixture of nitrous oxide and oxygen in a ratio of 3:1 is then given for a few minutes before ether is added. When light anaesthesia is obtained, the trachea is intubated with a short Magill endotracheal catheter. A slow infusion of citrated blood is started. The patient is placed in a lateral position and draped in a manner which allows the anesthetist an unobstructed view of the operative site. A few minutes before the pleura is entered, positive pressure is built up to 5 or 6 mm. of mercury. This prevents rapid collapse of the exposed lung. Later, this pressure is gradually lowered. The tracheobronchial tree is aspirated frequently with a catheter 45 cm. long. The anesthetist watches the diaphragm closely; jerky movements are the earliest sign of tracheobronchial obstruction

or mediastinal flutter. Aspiration is then performed; if this does not help, the pressure is built up to 4 or 5 mm. of mercury. Every half hour the surgeon pauses for one to two minutes while the unoperated lobes are re-expanded. Thus, inadvertent ligation of uninvolved bronchi is detected. Blood is given according to the amount lost; this averages 1,000 to 1,500 cc. After the diseased lung has been removed, the tracheobronchial tree is aspirated. The remaining portion of the lung is then re-expanded slowly. The anesthetists engaged in major thoracic surgery should be able to pass a bronchoscope with the patient lying in a lateral position. After the chest is closed, the patient is turned on his back and water bottles are attached to the drainage tubes. The bronchoscope is then passed and a vigorous stream of oxygen is sent through it. Roentgenograms of the chest are taken while the patient is still in the operating room. The patient remains until the films are developed. If these show persistent collapse, then bronchoscopy is repeated.—*Anesthesia in the surgical treatment of bronchiectasis, L. H. Mousel, New England J. Med., January 29, 1948, 238: 148.*— (*A. G. Cohen*)

Antimicrobial Therapy

Streptomycin for Tuberculous Meningitis.—In the Salpetrière Hospital in Paris 147 children with tuberculous meningitis were treated in the course of two years. The over-all recovery rate was only 29.2 per cent, but in the beginning many cases arrived for treatment in a desperate state. During the follow-up period of four to twenty months, none of the recovered patients exhibited any sequelae. Of the patients with meningitis alone, 33 per cent recovered; of those with meningitis associated with miliary tuberculosis, 25 per cent survived. There were no survivers among the patients in whom meningitis occurred as a later complication of miliary tuberculosis. Results have improved during the past two years with modification of the treatment. In the beginning streptomycin was administered discontinuously, the patients receiving 2 or 3 series lasting one month each. Only a small number of intrathecal injections were given. On this regimen, 17.5 per cent of the cases were arrested. At present treatment is continued until the spinal fluid cell count is less than 10. Children rarely relapse after the cell count reaches this level. Daily intrathecal injections are given during the first month. The dosage was 2.0 Gm. twice daily intramuscularly and 12 to 50 mg. intrathecally. The percentage of recoveries in this series was 47.5 per cent. The administration of streptomycin together with a sulfone compound raised the recovery rate further to 59 per cent in a series of 18 patients.—*Résultats de 2 ans de traitement de la meningite tuberculeuse de l'enfant, M. J. Fouquet, V. Heimann, M. Meyer & Hennequet, Presse méd., April 23, 1949, 57: 372.*—(*V. Leites*)

Streptomycin for Tuberculous Meningitis.—Of 76 admissions for tuberculous meningitis, 67 patients proved to have the disease; the remaining 9 had suggestive symptoms but the diagnosis was not substantiated. Prompt diagnosis is important, mental apathy being an early sign. In 3 patients the cerebrospinal fluid was normal early in the disease. When they occur, a fall in sugar, a rise in protein, and pleocytosis of the fluid are important diagnostic signs. Acid-fast bacilli were seen in the cerebrospinal fluid from 39 patients (58 per cent) prior to and within 48 hours of admission. Tubercle bacilli were recovered by culture or guinea pig inoculation of the fluid in 58 cases (87 per cent). Diagnosis by one or both of these criteria was established in 62 cases (92 per cent). The Mantoux test was positive in 50 of 51 patients tested; chest roentgenograms showed abnormalities in 50 of 66 patients. Forty patients received combined intrathecal and intramuscular streptomycin; 15 (37 per cent) of them survived. Ten others received intramuscular therapy only and 2 survived. Four patients received intramuscular therapy followed by combined therapy; one survived. Important factors contributing to therapeutic failure are vascular changes in the brain and hydrocephalus.

In 10 patients, a tube was inserted into the lateral ventricle to relieve the intracranial fluid pressure; only one of these patients survived. Strains of *M. tuberculosis* isolated from 43 of the patients have shown no resistance to streptomycin. Of the entire series, 18 patients (33 per cent) survived with complete clinical recovery in 16. Two have had relapses and show definitely abnormal cerebrospinal fluid.—*Tuberculous meningitis, J. Rubie & A. F. Mohun, Brit. M. J., February 26, 1949, No. 4599: 333.*—(*R. W. Clarke*)

Streptomycin for Enteric Tuberculosis.—The rapid effect of streptomycin on the clinical symptoms and roentgenological changes of intestinal tuberculosis was demonstrated in 8 cases. Complete regression or very marked improvement was noted in all but one patient who died of a pulmonary hemorrhage while under treatment. Four to six weeks of treatment with streptomycin in daily doses of 1.5 to 2 Gm. were sufficient to produce the desired result. However, the pulmonary pathology often necessitated longer administration.—*Efficacité de la streptomycine sur la tuberculose intestinale, P. Damade, F. Piéchaud, F. J. Traissac, P. Fréour, & M. Roux, Rev. de la tuberc., 1949, 13: 335.*—(*V. Leites*)

Streptomycin for Bone and Joint Tuberculosis.—The use of streptomycin for bone and joint tuberculosis was investigated by various French clinics under the auspices of the Ministry of Health. About 300 patients with proved tuberculous lesions which were not improving have been under treatment for six to ten months. Local and general treatment was continued and streptomycin was given in daily doses of 1.0 Gm. for adults, 0.25 Gm. for children below the age of five, and 0.5 Gm. for children five to fifteen years of age. Treatment was continued for 120 days during which no other chemotherapeutic agent was given. The reports show that: (*1*) An extremely favorable effect of streptomycin on the general condition and on constitutional symptoms was often noted. It was sometimes dramatic in severely cachectic patients. (*2*) The healing of fistulas was usually successful. Fistulas which had drained as long as nineteen years closed rapidly. (*3*) The effect on cold abscesses was less constant. Some observers reported no success, others had favorable results in a few patients after prolonged treatment. (*4*) No definitive conclusions were reached on the effect of streptomycin on the course of the osteo-articular lesions. It was felt by most observers that streptomycin had a rapid effect if given early, before bone destruction; more advanced lesions required surgery. Necessary operations were simplified by the preoperative administration of streptomycin and cases previously considered too far advanced for intervention were operated upon successfully after treatment. Lesions treated with streptomycin sometimes were found bacteriologically sterile at operation. There was also a favorable effect on the postoperative course.—*Streptomycine et tuberculose ostéo-articularie, M. E. Sorrel & Sorrel-Dejerine; Premiers resultats de l'emploi de la streptomycine dans le traitement des tuberculoses ostéo-articulaires, E. Bernard, P. Padavani & A. Lotte; Dix mois de streptomycine dans les localisations ostéo-articularies de la tuberculose, P. Gerard-Marchand; Premiers essais de traitement des tuberculoses ostéo-articulaires par la streptomycine, P. Ingelrans, A. Vendeuvre & J. Nigoul: Streptomycine et évolution de la tuberculose osseuse, M. Galland: Effets immediats d'un traitement de quatre mois par la streptomycine sur les tuberculeux osseux et ganglionnaires, R. Serée, H. Dettloff, P. Hubert & H. Verney: Le traitement des tuberculoses chirurgicales par la streptomycine, J. Bastide, J. Arrighi de Casanova, P. Roussel, Monfajon, Ch. Albaret, Semaine d. hôp. Paris, May 10, 1949, 25: 1491.*—(*V. Leites*)

Streptomycin with Extrapleural Pneumothorax.—Extrapleural pneumothorax was performed in 65 patients in 1947 and 1948, 32 of them receiving streptomycin preoperatively. The others were operated upon before streptomycin became available. In the streptomycin-

treated group there was one case of tuberculous effusion whereas in the untreated group tuberculous effusions occurred in 15 cases. The patients who developed fluid in the extrapleural space were subsequently treated with local injections of streptomycin 1.0 Gm. daily for 15 to 20 days. In 10 cases of the 15, there was complete absorption of fluid. In the remaining 5 cases, the fluid became sterile and serofibrinous after a few weeks.—*Les épanchements purulents tuberculeux des P.N.E.P. et streptomycine, Le Foyer, Bertheau, Perrès & Sabiani, Rev. de la tuberc., 1949, 13: 129.*—(*V. Leites*)

Streptomycin and Surgery.—The indications for the use of streptomycin in association with the surgical treatment of pulmonary tuberculosis are divided into 6 groups: (*1*) Acute pneumonic or bronchopneumonic cases as well as subacute cases with extensive nodular dissemination are at the onset strictly "medical" cases. If streptomycin is effective, these cases may become eligible for surgery in order to control remaining cavitary lesions. (*2*) Many chronic cavitary cases are unacceptable for surgery because of contralateral disease. These may be good surgical risks after regression of the contralateral lesions following streptomycin. (*3*) In some cavitary cases surgery is prevented by a very unfavorable clinical course with fever, weight loss, and abundant expectoration. Streptomycin may "cool off" the process and reduce expectoration so that surgery can be performed with a gain in time and safety. (*4*) In uncomplicated cases with none of the above mentioned contraindications to thoracoplasty, routine administration of streptomycin is not felt to be indispensable and, if decided upon, the course should not exceed two weeks. The routine use of streptomycin is more justified before extrapleural pneumothorax. (*5*) Preoperative and postoperative treatment with streptomycin is recommended as a routine procedure in excisional surgery. (*6*) Streptomycin has been of great help in such postoperative complications as extension of the tuberculous process in the lung, tuberculous extrapleural effusions, and chest wall fistulas.—*Sur les indications diverses et les modalités d'emploi de la streptomycine en association avec la collapsothérapie chirurgicale, E. Bernard, A. Lotte, J. Weill, R. Monod, Mathey & Monod. Rev. de la tuberc., 1949, 13: 1.*—(*V. Leites*)

Streptomycin Resistance of Tubercle Bacilli.—Tubercle bacilli from 39 patients were tested for streptomycin resistance before, during, and after treatment of the patients for 90 to 180 days with streptomycin 1 Gm. daily in two doses twelve hours apart. None of the 32 strains tested was resistant to 2.5 γ per cc. At the end of 30 days of treatment, no resistant strains were found in any of 30 patients. At the end of 60 days, 13 per cent of 24 patients had resistant bacilli. After 90 days, 29 per cent of 28 patients; and after 100 to 120 days, 45 per cent of 31 patients, had streptomycin-resistant strains. The number of resistant bacilli increased after cessation of treatment in 4 patients. It would seem advisable, therefore, to postpone final decision on the number of strains which become resistant until several months after the completion of streptomycin therapy. The average serum concentration of streptomycin was found to drop rapidly from 33 γ per cc. at two hours to 8.6 γ per cc. at eight hours and then more slowly to 1.7 γ per cc. at twelve hours after injection.—*Resistance of the tubercle bacillus to streptomycin, B. Blattberg & H. Ehrhorn, J. Lab. and Clin. Med., March, 1949, 34: 358.*—(*F. G. Petrik*)

Bacterial Reaction with Streptomycin Therapy.—In a series of 300 patients treated with streptomycin, 20 developed nausea, abdominal distention, vertigo, tachycardia, fever, and leukocytosis during the third or fourth week of treatment. When penicillin was given in addition to the streptomycin, all symptoms promptly disappeared. This reaction is neither an allergic nor a toxic one. It is due to a decided increase in the number of fecal streptococci.—*Streptococcus fecalis reaction occurring during streptomycin therapy,*

W. W. Stewart & O. L. Baldridge, J. A. M. A., February 26, 1949, 139: 579.—(H. Abeles)

Streptomycin for Respiratory Infections.—Streptomycin was given to 50 patients with various infections of the respiratory tract. Strikingly beneficial effects were obtained in 7 patients with pneumonia due to *K. pneumoniae*. Good results were seen in 3 patients with pneumonia due to *H. influenzae* and in 3 cases of pulmonary tularemia. There may have been some beneficial effect in one of 2 patients with coccal pneumonia. There was a questionable effect in 2 cases of pertussis with bronchopneumonia. One patient treated with streptomycin and penicillin survived pneumonia with agranulocytosis. There was no effect from the streptomycin treatment in one patient with atypical pneumonia and good response in one patient with virus pneumonia and a secondary *P. aeruginosa* infection. No effect was seen in 3 cases of asthma with chronic infection of the upper respiratory tract, in 6 cases of chronic bronchitis, nor in 8 cases of bronchiectasis. One case of actinomycosis showed a good response temporarily; sustained improvement was obtained in one patient with blastomycosis; no effect was seen in one patient with moniliasis. No effects from the streptomycin treatment were seen in 6 cases of sarcoidosis, 2 cases of Hodgkin's disease, nor in one case of silicosis.—*Streptomycin: Reports of its clinical effects in forty-four patients treated for various infections of the respiratory tract, E. J. Pulaski & Th. T. White, Arch. Int. Med., September, 1948, 82: 217.—(G. C. Leiner)*

Tuberculostatic Effect of Furacin.—A bacteriostatic effect of furacin on virulent human tubercle bacilli *in vitro* occurred with a concentration of 1:20,000 (5 mg. per 100 cc.) and a bactericidal effect with 1:5,000 (20 mg. per 100 cc.). However, the furacin, in the maximum tolerated dose of about 35 mg. per Kg. daily for 64 days, did not appreciably affect the course of tuberculosis produced in guinea pigs by the H37Rv strain. Resistance to furacin *in vitro* was not evident after many transfers of the H37Rv culture in drug-containing medium. The combination of Furacin and streptomycin in Tween-albumin liquid medium delayed, but did not prevent, the development of streptomycin-resistant bacilli of the H37Rv strain.—*Tuberculostatic effect of furacin in vitro and in vivo, E. Wolinsky, V. Wetzel, & W. Steenken, Jr., Proc. Soc. Exper. Biol. & Med., March, 1949, 70: 483.—(F. B. Seibert)*

Aureomycin for Primary Atypical Pneumonia.—A controlled series of 22 patients with primary atypical pneumonia were treated with aureomycin. Treatment was instituted with an intravenous injection of aureomycin hydrochloride 50 mg. and an oral dose of aureomycin 1.0 Gm. Thereafter, each patient received aureomycin 1.0 Gm. every six hours until his temperature had been normal for at least 48 hours. Nausea and vomiting were frequent after oral administration of the drug but never followed an intravenous injection. All patients responded uniformly well; defervescence was extraordinarily rapid in the majority. Relapse occurred in 3 patients after treatment was stopped and aureomycin was as effective in treating the relapse as the initial episode. A control group of 20 patients was treated with penicillin; prompt recovery occurred in almost half of this group. Aureomycin treatment resulted in the prompt recovery of all patients and it can be considered highly effective in primary atypical pneumonia.—*Aureomycin in primary atypical pneumonia: A controlled evaluation, G. Meiklejohn & R. I. Shragg, J. A. M. A., May 28, 1949, 140: 391.—(H. Abeles)*

Aureomycin for Tularemia.—Three patients with tularemia were treated with aureomycin. They responded promptly and the results are comparable to streptomycin therapy in the degree of effectiveness.—*Aureomycin in treatment of experimental and human tularemia, T. E. Woodward, W. T. Raby, W. Eppes, W. A. Holbrook & J. A. Hightower, J.A.M.A., March 26, 1949, 139: 830.—(H. Abeles)*

Laboratory Studies

Thiosemicarbazone in Experimental Tuberculosis.—The effect of a thiosemicarbazone, TB 1 698, prepared by Domagk and his collaborators in Germany, was studied in experimental tuberculosis of mice. Doses of 10 mg. were given orally for 46 days after intravenous infection with 1 mg. of a three-week-old culture of virulent tubercle bacilli. An untreated group of mice infected in the same manner served as controls. In the untreated group, all the animals died in 26 to 30 days. In the treated group, 41 per cent of the animals survived until the fifty-eighth day, when they were sacrificed. There was a marked decrease in the bacillary content of the lungs in the treated mice as compared to the untreated ones. The microscopic character of the lesions in the treated animals resembled that seen with streptomycin therapy but neither the length of survival nor the signs of healing were as good as those with streptomycin. The incidence of relapses was very high in spite of continuation of the daily treatment. The drug seemed to have its maximum antimicrobial effect at the onset of treatment and the proliferation of tubercle bacilli was marked after the forty-fifth day. The mode of action of thiosemicarbazone is considered analogous to that of p-aminosalicylic acid but its effectivity seems to be higher.—*Effets curatifs du Thiosémicarbazone (TB 1) dans la tuberculose experimentale de la souris, C. Levaditi, Presse méd., June 11, 1949, 57: 519.*—(*V. Leites*)

Nutrition and Response to Tuberculosis.—A controlled study was made of the physiological and pathological responses of protein-deficient rats to a tuberculous infection. The growth, food consumption, plasma proteins, hematologic variations, and tissue response were investigated. Young, growing rats were maintained on one of 3 diets: adequate, protein-deficient, or initially adequate and then acutely, severely deficient. Infection of these animals with *M. tuberculosis* H37Rv gave results which seem to favor the concept that dietary protein deficiency does not alter significantly the susceptibility of the rats nor the course of the tuberculosis. This seems to be true regardless of the severity or duration of the protein deficiency; it apparently makes no difference whether the previous protein intake was high or low. Changes in the white blood cell count, hemoglobin and plasma proteins were consistent with those in uninfected, protein-deficient rats and were not peculiar to the tuberculous animals. There were equivocal changes in the myeloid-erythroid ratio of the marrow in infected animals. Tuberculous rats had an apparent increase in the alpha and beta globulins but this was not evident when the unit-circulating quantities of the plasma components were estimated.—*Nutritional status and infection response. II. Electrophoretic, circulating plasma protein, hematologic, hematopoietic, and pathologic responses to mycobacterium tuberculosis (H37Rv) infection in the protein-deficient rat, J. Metcoff, D. Darling, D. Wilson, A. Lapi & F. J. Stare, J. Lab. & Clin. Med., March, 1949, 34:* 335.—(*F. G. Petrik*)

Test of Streptomycin Sensivity.—Rapid evaluation of streptomycin sensitivity is possible by direct culture of the pathological specimen on solid and liquid media containing graduated concentrations of streptomycin. Incipient growth can be demonstrated as early as on the fifth or sixth day by microscopic examination of slides obtained from the inoculated media. This method may not be absolutely accurate but it is considered adequate and valuable for clinical purposes.—*Évaluation rapide de la streptomycino-resistance par la culture directe des produits bacillifères, J. Bretey, P. J. Coletsos & H. Boisvert, Ann. Inst. Pasteur, February, 1949, 76, 188.*—(V. *Leites*)

Streptomycin-dependent *M. Ranae*.—A new streptomycin-dependent variant of *Mycobacterium ranae* has been isolated. It will grow only in low concentrations of streptomycin. Parent-type cells which grow without streptomycin were isolated from several streptomycin-dependent strains. The number of parent-type cells found varied with the size

and character of the population and with the concentration of streptomycin in which the dependent cells were growing. Detailed studies failed to reveal any differences between the parent-type cells found in the streptomycin-dependent cultures and the cells of the original parent population. This is believed to be an example of reverse mutation. Attempts to induce changes in the incidence of parent-type cells in streptomycin-dependent populations were unsuccessful. Streptomycin-dependent and streptomycin-resistant cells were grown in the same culture and after several successive subcultures the presence of streptomycin-dependent cells could not be readily detected.—*The biological characteristics of streptomycin-dependent Mycobacterium ranae, D. Yegian & R. J. Vanderlinde. J. Bact., February, 1949, 57: 169.—(F. G. Petrik)*

Culture of Tubercle Bacilli.—The addition to the medium of relatively small amounts of horse serum (1:30) modifies considerably the cultural characteristics of tubercle bacilli. In the simple Sauton medium, tubercle bacilli grow very poorly in the depth of the medium and have a tendency to develop on the surface. Under the influence of serum, the tubercle bacilli become more anaerobic and grow in the depth of the liquid medium as early as the sixth day after inoculation with a small number of bacilli. In the presence of serum this growth in the depth takes place either in the presence or absence of glycerine. Sauton medium with horse serum has proved very useful and inexpensive for titration of certain antibiotics, the results being comparable to those obtained with the media of Dubos and Youmans.—*Culture en profondeur de bacille tuberculeux en milieu de Sauton additionné de sérum de cheval et titrage de certains antibiotiques. J. Solomidès, Ann. Inst. Pasteur, April, 1949, 76: 371.—(V. Leites)*

Transfer of Systemic Tuberculin Sensitivity.—Systemic tuberculin sensitivity could be passively transferred in guinea pigs by means of the cells of induced peritoneal exudates from tuberculous donors. The systemic shock induced in these recipients was of the typical delayed tuberculin type. Desensitization of some tuberculous donors with tuberculin abolished the capacity of their peritoneal cells to passively transfer the tuberculin sensitivity. This evidence indicates that desensitization results from the saturation of fixed cellular antibody with antigen.—*Tuberculin reaction: III. Transfer of systemic tuberculin sensitivity with cells of tuberculous guinea pigs, W. F. Kirchheimer, R. L. Weiser, & R. Van Liew, Proc. Soc. Exper. Biol. & Med., January, 1949, 70: 99.—(F. B. Seibert)*

Leukocyte Blockade of Tuberculin Cytolysis.—Suspensions of white blood cells from normal persons with a negative intracutaneous tuberculin reaction, as well as those from patients with active tuberculosis, adsorbed tuberculin (OT) from the plasma. The tuberculin was assayed by its *in vitro* cytotoxic effect on the white blood cells of tuberculous subjects. White blood cells from normal or tuberculous mice did not adsorb tuberculin. Plasma from patients with active tuberculosis partially inactivated tuberculin whereas normal human plasma did not. *Leukocyte blockade of in vitro tuberculin cytolysis, C. B. Favour, Proc. Soc. Exper. Biol. & Med., February, 1949, 70: 369.—(F. B. Seibert)*

Pulmonary Edema due to ANTU.—Dogs under nembutal anesthesia were given alpha-naphthyl thiourea (ANTU) intravenously in propylene glycol. When one cc. per Kg. of a 2 per cent solution was injected, the animals developed fatal pulmonary edema. The first evidence of changes leading to edema was an increase in the flow of lung lymph. Greater rate and minute volume of breathing followed. Blood gas analyses indicated that the hyperpnea of rapidly developing pulmonary edema was peripheral in origin.—*Acute effects upon the lungs of dogs of large intravenous doses of alpha-naphthyl thiourea (ANTU), C. K. Drinker & E. Hardenbergh Am. J. Physiol., January, 1949, 156: 35.—(G. C. Leiner)*

Pulmonary Edema and Intracranial Pressure.—Increased intracranial pressure was produced in 24 guinea pigs five minutes before they were guillotined. In approximately one-half of them pulmonary edema, congestion, and hemorrhage were found, and the lung weight/body weight and lung weight/heart ventricle weight ratios were elevated. Bilateral cervical vagotomy exerted a protective effect against pulmonary edema subsequent to elevation in intracranial pressure.—*Pulmonary lesions in guinea pigs with increased intracranial pressure, and the effect of bilateral cervical vagotomy, G. S. Campbell & M. B. Visscher, Am. J. Physiol. April 1949, 157: 130.—(G. C. Leiner)*

Fluid Shifts in Pressure Breathing.—A method has been developed for exposing anesthetized animals to high positive pressure respiration, using a counter-pressurization system and a simple helmet. Animals exposed to pressure breathing show a rapid loss of fluid from the circulation which is roughly proportional to the mean respiratory pressure employed. Protein leakage was inconstantly observed in animals exposed to pressure breathing.—*Fluid shifts in animals during pressure breathing, Ch. Mann & J. Goodman, Am. J. Physiol., October, 1948, 155: 208.—(G. C. Leiner)*

Respiration after Pulmonary Artery Ligation.—From experiments in dogs in which the left pulmonary artery had been ligated the following conclusions were made: "A lung with a ligated pulmonary artery can maintain a respiratory function. The capacity of such a lung to absorb oxygen gradually increases over a period of months. When oxygen rather than air is supplied through a bronchospirometric cannula, while the intact lung continues to breathe air, the oxygen content of the arterial blood is found to rise. The effective flow in the bronchial arteries of such a lung increases with time after ligation, as measured by bronchospirometry and an application of the Fick principle. The increase in circulation is in step with the expansion of the vascular bed demonstrated in anatomical studies by the vinylite method as reported elsewhere. This flow is largely a burden on the left heart whose output becomes roughly one-third greater than that of the right. A similar situation obtains in human disease, such as bronchiectasis or congenital pulmonic stenosis, where there is an extensive collateral circulation to the lungs."—*Respiratory function and blood flow in the bronchial artery after ligation of the pulmonary artery, W. E. Bloomer, W. Harrison, G. E. Lindskog, & A. A. Liebow, Am. J. Physiol., May, 1949, 157: 317.—(G. C. Leiner)*

Pulmonary Infarction.—Obstruction of branches of the pulmonary artery results in infraction only when there is interference with the collateral circulation at the same time. Pulmonary embolisms were produced in dogs by releasing blood clots from the jugular veins; no infarctions developed. Pulmonary congestion was produced in 8 dogs by the intravenous administration of alpha-naphthylthiourea prior to the release of emboli; 3 developed pulmonary infarction distal to the embolism and 4 had alveolar hemorrhage distal to the embolism.—*Experimental pulmonary infarction: Abnormal pulmonary circulation as a prerequisite for pulmonary infarction following an embolism, D. W. Chapman, L. J. Gugle & P. W. Wheeler, Arch. Int. Med., February, 1949, 83: 158.—(G. C. Leiner)*

Resuscitation from Obstructive Asphyxia.—Obstructive asphyxia was produced in dogs and different methods for resuscitation were tested. When no treatment was given, 32 per cent of 22 dogs survived. Of 20 dogs given manual artificial respiration in air, 35 per cent survived. When mechanical artificial respiration in air was used, 75 per cent of 20 dogs survived. With mechanical artificial respiration and 100 per cent oxygen, 71 per cent of 21 dogs survived. When mechanical artificial respiration was used with a mixture of 7 per cent CO_2 and 93 per cent O_2, 85 per cent of 20 dogs survived.—*Resuscitation from obstructive asphyxia, H. Schwerma, A. C. Ivy,*

W. L. Burkhardt & A. F. Thometz, Am. J. Physiol., February, 1949, 156:$\frac{7}{4}$*145.—(G. C. Leiner)*

Experimental Pulmonary Atelectasis.—Atelectasis occurs in a part of the lung when the bronchus leading to it is completely occluded as happens frequently during various pathological processes. In such cases the air in the occluded segment is resorbed. Atelectasis also occurs when a bronchus is partially occluded by an obstacle which acts as a valve permitting expiration from, but not inspiration into, a part of the lung. In this circumstance, air is both expired and absorbed. Lesions which act in this fashion are very rare; more often the obstacle in the bronchus permits inspiration but no expiration so that emphysema results. Collapse therapy as used in the treatment of pulmonary tuberculosis seeks to reduce the air content of cavities and to produce atelectasis of the surrounding lung parenchyma. Anything which induces emphysema or prevents drainage of secretions from the collapsed area interferes with the treatment. Experimental pulmonary atelectasis was produced in dogs by the authors who introduced a metal check valve through the Chevalier Jackson bronchoscope into the bronchus of one lower lobe. The valve used permitted both the expiration of air and the evacuation of bronchial secretions from beyond the obstruction. The resultant atelectasis did not produce signs on physical or roentgenographic examination although the area was demonstrable at post-mortem examination. When the valve was inverted, emphysema resulted but this also was demonstrable only by dissection. These results suggest a means of producing therapeutic localized atelectasis with free drainage of secretions. There are many technical difficulties, however, especially when the attempt is made to occlude an upper bronchus. Some means of decreasing the reaction of the bronchial tissue to the foreign body were found and are being studied further.—*Experiment atelectasis of the lungs by bronchial obstruction* (*Slovak*), *Z. Scheiner & M. Cara, Rozhledy v Tuberculose, 1948, 8: 94*—(*J. Ilavsky*)

Gas Exchange in Respiratory Dead Space.—In 2 healthy adults, air samples from the supraglottic portion of the respiratory dead space were analyzed. Within one to two seconds during breath-holding after the end of an inspiration, a small rise in carbon dioxide tension and fall in oxygen tension were found. When the breath was held at the end of an inspiration for progressively longer periods, the carbon dioxide concentration increased at a nearly steady state, whereas the oxygen concentration fell only during the first ten seconds. It is believed that the gas exchange occurs across the mixed glandular secretions which bathe the supraglottic area.—*Study of the exchange of oxygen and carbon dioxide in the supraglottic portion of the respiratory dead space, M. Galdston & S. A. Horwitz, Am. J. Physiol., December, 1948, 155: 420.—(G. C. Leiner)*

Artificial Respiration and Altitude.—Five types of artificial respiration were evaluated in rats at Denver's altitude and at an altitude of 40,000 feet. The types studied were: Eve tilt board, Schafer prone pressure, Pulmotor or 'suck and blow' type, Drinker respirator, and Thunberg barospirator. At high and low altitudes the mechanical methods for artificial respiration were superior to manual methods. The Schafer method was more effective than the Eve method. The administration of oxygen while giving artificial respiration at high altitudes proved especially beneficial to the circulation. This was particularly true with the barospirator which was the most effective method studied for restoring the circulation. Since the circulatory response always occurred first, this was important in bringing about the resumption of respiration. Low temperatures had a better effect than the administration of oxygen carbon dioxide mixtures. Coramine proved effective in stimulating respiration at low altitudes but not at high. Strychnine also was effective, but caffeine, picrotoxin, metrazol,

and potassium cyanide had little effect.—*Efficiency of various types of artificial respiration at high altitudes, F. R. Blood & F. E. D'Amour, Am. J. Physiol., January 1949, 156: 52.*—(*G. C. Leiner*)

Carbonic Anhydrase in Blood.—With a new method, measurements of carbonic anhydrase activity of the blood were made in 40 patients with dyspnea due to cardiac or pulmonary diseases, and in one patient with obstruction of the superior vena cava. The anhydrase activity always was normal in relation to hematocrit value, erythrocyte count, and hemoglobin concentration. It was increased in patients with polycythemia due to pulmonary disease and in patients with increased blood volumes due to congestive failure.—*Activity of carbon anydrase in the blood: Study of patients with dyspnea consequent to chronic cardiac and pulmonary disease, M. D. Altschule & H. D. Lewis, Arch. Int. Med., May 1949, 83: 547.*—(*G. C. Leiner*)

Public Health and Epidemiology

Reaction to Vole Tubercle Bacilli.—It has been shown that vole tubercle bacilli are only slightly pathogenic for rabbits and guinea pigs. Injection of caseous material from lesions of naturally infected voles or of living vole tubercle bacilli protects these animals against virulent mammalian tubercle bacilli. Pathogenicity of the vole organism for calves is low; its immunizing power is greater than that of BCG, all injected calves developing strongly positive tuberculin reactions. In the current study, 16 patients with far advanced tuberculosis were injected intradermally with 0.0001 mg. of a culture of living vole tubercle bacilli. A marked local reaction developed, consisting of a tiny red papule surrounded by an area of erythema. This slowly increased in size, reaching its maximum in ten days. In most cases, the papule became a pustule. There was no lymphadenopathy or constitutional reaction. The intensity of the reaction paralleled the Mantoux reaction. For injection in other cases, the bacilli were killed by heat; the reaction was slightly less intense but of the same character. When dosages up to 0.1 mg. were used, the same reactions were obtained but the intensity was in proportion to the dosage scale. In no case was a patient affected adversely.—*The intracutaneous injection of vole tubercle bacilli in tuberculous persons, C. Cameron & I. A. Purdie, Tubercle, December, 1946, 27: 195.*—(*A. G. Cohen*)

Vaccination with Vole Bacillus.—Vaccinations were carried out with the murine type of tubercle bacillus (vole bacillus) in 2 communities. A group of 444 persons with a low incidence of tuberculosis was tested; 116 were negative to intradermal tests with 0.1 cc. of Old Tuberculin 1:100. Forty-eight of the nonreactors were vaccinated. Only one case of tuberculosis developed in the control group and none appeared in the vaccinated group. After vaccination all of the latter became sensitive to 0.1 cc. of O.T. 1:100. Sensitivity to O.T. 1:10,000 appeared but gradually waned. In another community with a high incidence of tuberculosis, there were 179 nonreactors among 441 persons tested. Eighty-one of the nonreactors were vaccinated; one case of tuberculosis developed in this group. In the control group, there were 4 deaths and 4 other cases. This difference is statistically significant.—*Vaccination with the murine type of tubercle bacillus (vole bacillus), A. G. Wells, Lancet, July 9, 1949, 1: 53.*—(*A. G. Cohen*)

Tuberculosis in Belgian Congo.—The control of tuberculosis in the Congo has become more difficult since the war because of the rapid increase in population which has accompanied industrial development. Besides the native villages, many new, larger population centers have developed. There are now over 14,000,000 persons, mostly Negroes, in the Belgian Congo and Ruanda-Urundi. Adequate food and hygiene are more easily provided in the large groups under the direct management of rich and powerful industrial companies which are responsible for the workers' housing, food, education, and medical care. The central government must pro-

vide for other groups. A recent study showed that in certain mining locations 80 per cent of the workers and 64 per cent of their wives gave positive tuberculin reactions, as did 30 per cent of children up to fifteen years of age. Most cases of active tuberculosis were found in adolescents and young adults. Accurate mortality statistics were not available and it is impossible to say to what extent the disease is increasing or the population is gradually becoming immunized. Fulminating cases which soon cease to be centers of infection are less to be feared than the more chronic cases which are now increasing in number. Meningitis is rare; miliary tuberculosis occurs more often than it is diagnosed. Many cases of ulcerocaseous pulmonary tuberculosis are not diagnosed. Adolescents often die of a primary infection. The author emphasizes the area's need of trained physicians and advocates BCG vaccination of negative reactors exposed to infection.—*Les problèmes relatifs à la tuberculose chez les noirs au Congo belge en 1948, J. Firket, Acta Tuberculosea Belgica, February, 1949, 1: 3.—(A. T. Laird)*

Tuberculosis in Mental Hospitals.—In 1945 the resident population of the mental hospitals in California was 25,810, forming 0.3 per cent of the state's population and contributing 4.4 per cent of the deaths from tuberculosis. The death rate of 657 per 100,000 in mental hospitals and 361 in institutions for mental defectives compares with a total tuberculosis death rate of 43.4 for California. Contrary to popular belief, there is considerable patient movement in mental institutions. In 1944–1945 there were 8,703 admissions and 3,069 returned from parole or escape. There were 5,397 patients paroled and 2,524 discharged from parole in that year. Thus, any existing reservoir of infection in mental institutions constitutes a potential hazard to the nontuberculous resident patients and employees and to the population at large. During an eleven month survey begun in 1946, 25,914 chest photoroentgenograms were made of mental patients in 7 hospitals. Of these, 2,139, or 8.25 per cent, were found to have evidence of pulmonary tuberculosis. This represents previously unsuspected cases, inactive as well as active, but does not include calcified primary lesions, pleural effusions, or pleural thickening. Of 4,832 patients surveyed, 622 had been residents for a maximum of only six months and this prevalence (1.6 per cent) can be considered essentially the prevalence on admission. This is higher than general population surveys but is about the same as that found in general hospital admissions. The prevalence of tuberculosis in the group resident for five years or more was 8.8 per cent, in contrast to 3.0 per cent among those resident less than five years. Prevalence of tuberculosis was higher among patients with dementia praecox, probably because they are hospitalized longer and therefore have greater opportunity for exposure. Fifty-five per cent of the cases discovered were classified as minimal, 36 per cent as moderately advanced and 9 per cent as far advanced. One-seventh of the cases showed evidence of cavitation and another 5 per cent were suspicious. Among the far advanced cases 71 per cent had cavitation. The cavitary cases represent more than one per cent of the total resident population of the hospitals. Of 3,321 employees, 2.7 per cent had evidence of reinfection tuberculosis. In the hospitals showing a higher prevalence among patients, there was also a higher percentage of cases among employees. Conclusions reached were (*1*) all new admissions must be X-rayed, (*2*) all resident patients should have films taken, and (*3*) all patients with communicable tuberculosis should be segregated.—*Tuberculosis control program of nine California mental institutions (results of initial chest X-ray survey), W. R. Oechsli, U. S. Pub. Health Rep., January 7, 1949, 64: 4.—(E. A. Rouff).*

Tuberculosis Control.—The U. S. Public Health Service is engaged in the following tuberculosis control activities: (*1*) Roentgenographic surveys in 92 American cities with populations over 100,000. An attempt is made to obtain a chest roentgenogram of every individual over the age of 15 in each community. Of the lesions which required further study,

80 per cent were unknown before the survey. (*2*) Investigations on BCG as an immunizing agent against tuberculosis. The various methods of administering the vaccine are being evaluated. Attention is called to the importance of special control measures to be taken in mental hospitals where the mortality from tuberculosis is often 10 times the rate for the general population. Surveys of the tuberculosis control activities in the various states reveal a great divergence in the efficacy of the different control programs. The U. S. Public Health Service supplements the activities of the states, where necessary.—*Summary of tuberculosis control activities, F. J. Weber & R. J. Anderson, Am. J. Pub. Health, April, 1948, 38:* 512.—(*M. B. Lurie*)

Eradication of Tuberculosis.—The tuberculosis mortality in Minnesota was reduced from 120 per 100,000 in 1911 to 20 in 1947. This was accomplished by: (*1*) isolating infectious cases, (*2*) tracing the sources of contagion for ill children and adults, (*3*) eliminating exposure to infected domestic animals, and (*4*) using roentgenographic surveys. In the past 30 years, the mortality in children was reduced by 88 per cent, and in infants by 93 per cent. The morbidity from tuberculosis is so reduced that many beds in the state sanatoriums are vacant. In the twenties and thirties many student nurses in the medical school developed tuberculosis; this is a rare occurrence at present. Furthermore, the attack rate was as high as 100 per cent among the non-reacting nurses; it is now only 5 per cent. Thirty-three per cent of beginning medical students reacted to tuberculin in 1928; in 1946 only 6 per cent were positive. The rate of positive reactions in grade school children has declined from 47 to 7 per cent in a similar period.—*Eradication of tuberculosis by epidemiological methods, J. A. Myers, Am. J. Pub. Health, April 1948, 38: 516.*—(*M. B. Lurie*)

Relapse in Pulmonary Tuberculosis.—A five year follow-up study was made of 256 patients whose sputum had contained tubercle bacilli. Of these, 73 had been discharged as recovered to return to full work; 52 as quiescent to resume full work; 17 with active disease to do full work; 35 with limited working capacity to have various stages of activity; and 79 others, including those totally incapacitated. In the recovered group, 8 cases relapsed. In the quiescent group, one-third recovered, another third remained quiescent, and the remainder deteriorated. Of the patients with active disease who returned to full work, one-half died. Since 10 per cent of "recovered" cases break down within five years, more may relapse later, suggesting that a constant check is necessary. In 9 of a group of 14 relapsed cases which were studied closely, there were features of the patients' life situation which were conducive to breakdown. A case of tuberculosis must be considered a long-term liability from the viewpoint of working capacity.—*Relapse in pulmonary tuberculosis, W. Tattersall, Tubercle, April, 1949, 30: 74.*—(*A. G. Cohen*)

Rehabilitation of Tuberculous Patients.—The author conducts a resettlement clinic for tuberculous outpatients in Wallasley, a borough with a population of about 100,000. A "score card" is made up for each new patient. Its components, with the maximum grade for each, are: prognostic index 50, respiratory and circulatory index 20, work index 10, and home index 10. This is used only as a guide since each case has to be considered individually. A large proportion of persons with pulmonary tuberculosis are capable of working in industry and no single factor determines employability. A positive sputum reduces it but is not *per se* disabling. After discharge from the sanatorium, the patient attends a sheltered workshop until he graduates into ordinary industry.—*Reablement of tuberculous patients, R. Grenville-Mathers, Lancet, April 2, 1949, 1: 463.*—(*A. G. Cohen*)

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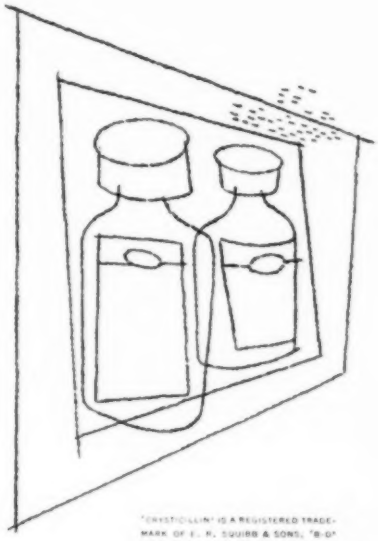

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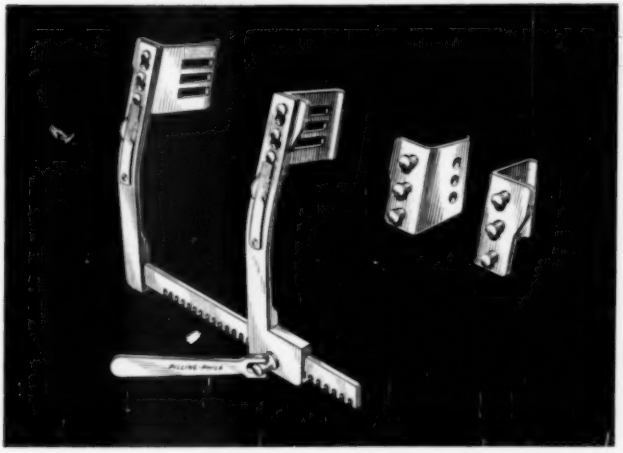

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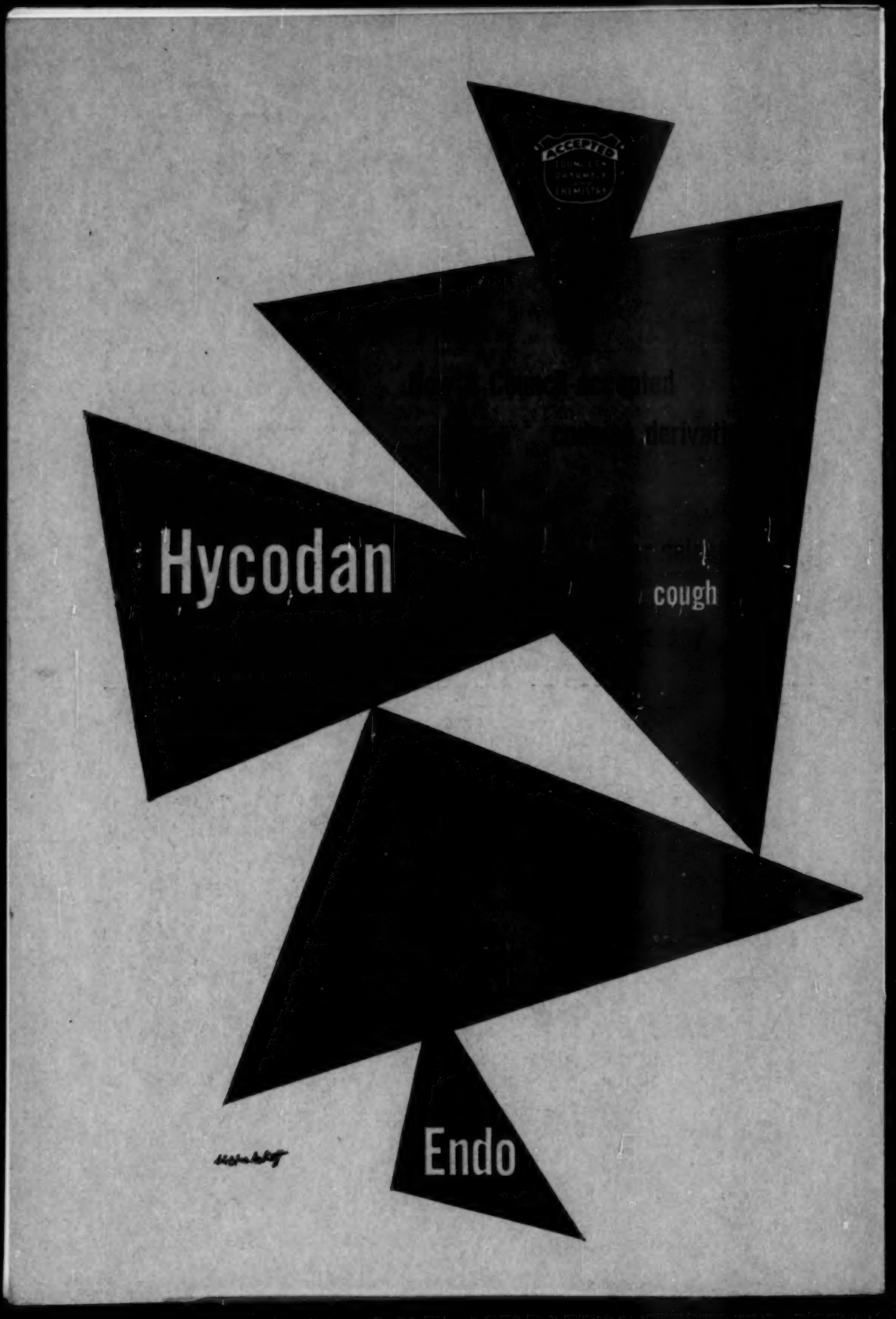
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